U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

01-776

# SEARCH REQUEST FORM

Requestor's Name: Jeffrey E. Russel

Serial Number: PCT/US98/25964

Date: 1-26-1999 Phone: 308-3975 Art Unit: 1654

9807

**Search Topic:**

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevent citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevent claim(s).

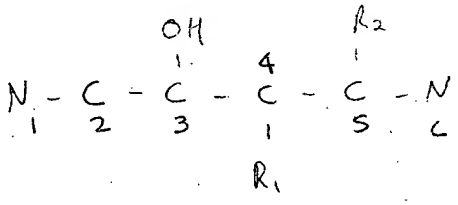
Please search the partial structures below and attached.

Keywords are HIV and protease inhibitor.

Thank you.

JER

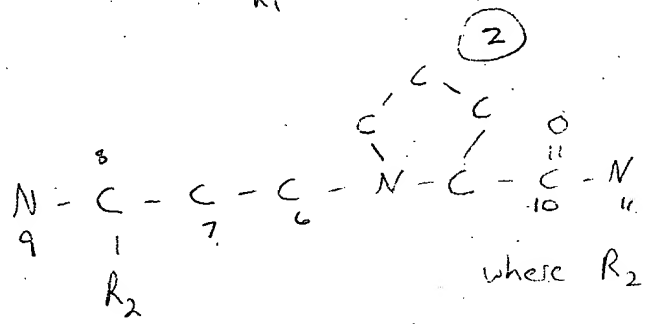
(1)




where $R_1$ = H or OH

$R_2$ = alkyl or $-CH_2-$ (O) (10)

(2)




where $R_2$ = alkyl or $-CH_2-$ (O)

$10.65 @5

## STAFF USE ONLY

Date completed: 01-29-99

Searcher: Beverly @4994

Terminal time: 40

Elapsed time:

CPU time:

Total time: 55

Number of Searches:

Number of Databases: 1

**Search Site**

_____ STIC

_____ CM-1

_____ Pre-S

**Type of Search**

_____ N.A. Sequence

_____ A.A. Sequence

_____ Structure

_____ Bibliographic

**Vendors**

_____ IG

✓ STN

_____ Dialog

_____ APS

_____ Geninfo

_____ SDC

_____ DARC/Questel

_____ Other

Russel, J.
PCT/25964



FILE 'REGISTRY' ENTERED AT 12:05:55 ON 29 JAN 1999
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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STRUCTURE FILE UPDATES: 23 JAN 99 HIGHEST RN 217939-24-7
DICTIONARY FILE UPDATES: 28 JAN 99 HIGHEST RN 217939-24-7

TSCA INFORMATION NOW CURRENT THROUGH JUNE 29, 1998

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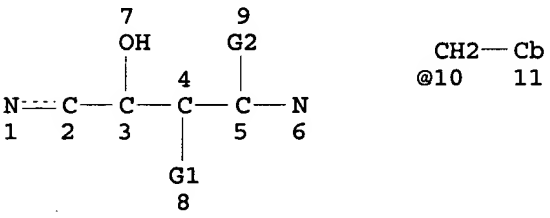
=> d que stat; fil caplu; s l6 or l6/d

L1 STR

Str. 1

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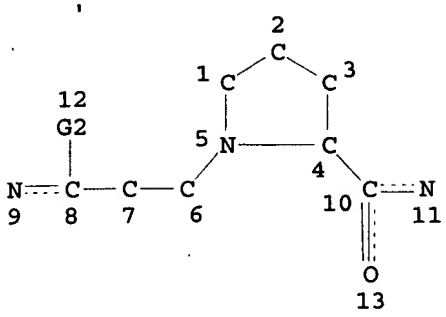
GGCAT IS UNS AT 11
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 11

STEREO ATTRIBUTES: NONE
L2 STR




Str. 2

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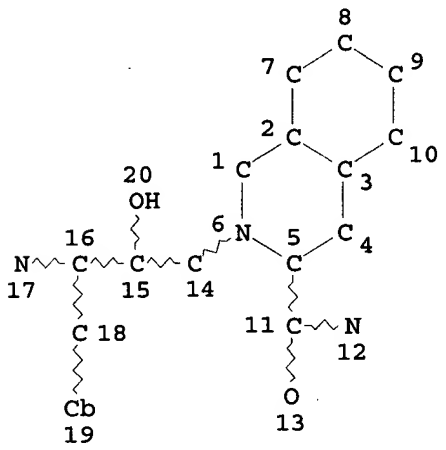
GGCAT IS UNS AT 15
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE
L3 STR



Str. 3

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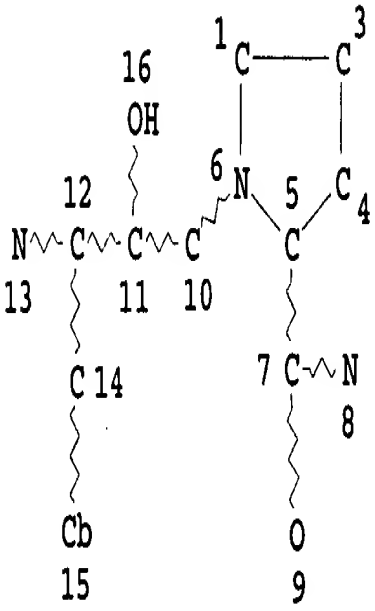
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE

L4 STR

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DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

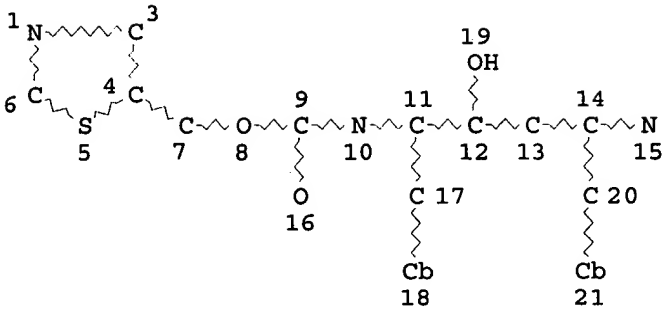
NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE

L5 STR

Searcher : Shears 308-4994

Str. 5




NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L6 2575 SEA FILE=REGISTRY SSS FUL L1 OR L2 OR L3 OR L4 OR L5

Temp saved 7 days.

100.0% PROCESSED 172527 ITERATIONS 2575 ANSWERS
SEARCH TIME: 00.01.42

FILE 'CAPLUS' ENTERED AT 12:09:01 ON 29 JAN 1999
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1967 - 29 Jan 1999 VOL 130 ISS 5
FILE LAST UPDATED: 29 Jan 1999 (19990129/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

Searcher : Shears 308-4994

565 L6
24 L6/D
L7 565 L6 OR L6/D

L8 1764 SEA ABB=ON PLU=ON ((PROTEINASE OR PROTEASE)(W)INHIBIT?) (3A)(FIV# OR HIV# OR HTLV# OR (HUMAN OR FELINE)(3W)VIRUS? OR IMMUN?(1W)VIRUS? OR AIDS OR ACQUIR?(2W)SYNDROM?)
L9 82 SEA ABB=ON PLU=ON L7(3A)L8

=> d 1-82 .bevstr

L9 ANSWER 1 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1999:23648 CAPLUS
TI Development of HIV protease inhibitors. A survey
AU Ren, Shijun; Lien, Eric J.
CS Dep. Pharmaceutical Sciences, School Pharmacy, Univ. Southern California, Los Angeles, CA, 90033, USA
SO Prog. Drug Res. (1998), 51, 1-31
CODEN: FAZMAE; ISSN: 0071-786X
PB Birkhaeuser Verlag
DT Journal; General Review
LA English
AB A review with 63 refs., describing the development of human immunodeficiency virus (HIV) protease inhibitors as antiviral agents against HIV, structure-activity relationship anal. of saquinavir and related compds., comparison of the HIV protease inhibitors saquinavir, ritonavir, indinavir, and nelfinavir, and future prospect in developing new anti-HIV drugs.
IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(development of **HIV protease inhibitors**)

L9 ANSWER 2 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1998:674195 CAPLUS
TI Protease inhibitors and adipocyte differentiation in cell culture
AU Gagnon, AnneMarie; Angel, Jonathan B.; Sorisky, Alexander
CS OGH Research Institute, University of Ottawa, Ottawa, K1Y 4E9, Can.
SO Lancet (1998), 352(9133), 1032
CODEN: LANCAO; ISSN: 0140-6736
PB Lancet Ltd.
DT Journal
LA English
AB The effects of ritonavir and indinavir were tested in the preadipocyte cell line, murine 3T3-L1 cells. Both protease inhibitors enhanced adipogenesis by as much as 10-40%, and

ritonavir, for reasons unknown, may have a more potent effect. The mechanism by which protease inhibitors induce adipocyte differentiation is not clear. Understanding the adipogenic action of protease inhibitors should help to make their use as anti-HIV agents optimum while keeping side effects on adipose tissue, and perhaps the assocd. deleterious effects on glucose and fat metab. to a min.

IT **155213-67-5**, Ritonavir
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-**HIV protease inhibitors** and adipocyte differentiation in 3T3-L1 cell culture)

L9 ANSWER 3 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1998:523635 CAPLUS
DN 129:270017
TI HIV type 1 protease inhibitors fail to inhibit HTLV-I Gag processing in infected cells
AU Pettit, Steven C.; Sanchez, Ricardo; Smith, Terri; Wehbie, Robert; Derse, David; Swanstrom, Ronald
CS Lineberger Comprehensive Cancer, CB7295, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599, USA
SO AIDS Res. Hum. Retroviruses (1998), 14(11), 1007-1014
CODEN: ARHRE7; ISSN: 0889-2229
PB Mary Ann Liebert, Inc.
DT Journal
LA English
AB Protease inhibitors are currently the most effective antiviral agents against human immunodeficiency virus type 1 (HIV-1). In this study we detd. the effect of four HIV-1 protease inhibitors on human T cell leukemia virus type 1 (HTLV-I). Rhesus monkey cells infected with HTLV-I were treated with different concns. of indinavir, saquinavir, ritonavir, or nelfinavir. The effect of these inhibitors was monitored through their effect on the processing efficiency of the viral Gag protein in cells, the natural substrate for the viral protease. The inhibitors failed to block processing of HTLV-I Gag. To confirm these findings, human cells were cotransfected with plasmids encoding infectious copies of HIV-1 and HTLV-I, and the cells were subsequently treated with these same HIV-1 protease inhibitors. At concns. between 5 and 50 times the IC50 for inhibition of HIV-1 replication, inhibition of HIV-1 Gag cleavage was apparent. In contrast, no effect of HTLV-I Gag processing was seen. At higher concns., HIV-1 Gag processing was essentially completely inhibited whereas HTLV-I Gag cleavage was still unaffected. Thus, these inhibitors are not effective inhibitors of HTLV-I Gag processing. Sequence alignments of the HIV-1 and HTLV-I viral proteases and processing sites suggest that the active site of the HTLV-I protease may have subtle differences in substrate recognition compared with the HIV-1 protease.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**HIV** type 1 **protease inhibitors**
fail to inhibit HTLV-I Gag processing in infected cells)

L9 ANSWER 4 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1998:446895 CAPLUS
DN 129:203171
TI HIV-1 Protease Inhibitors Based on Acyclic Carbohydrates
AU Zuccarello, Guido; Bouzide, Abderrahim; Kvarnstroem, Ingemar; Niklasson, Gunilla; Svensson, Stefan C. T.; Brisander, Magnus; Danielsson, Helena; Nillroth, Ulrika; Karlen, Anders; Hallberg, Anders; Classon, Bjoern; Samuelsson, Bertil
CS Department of Chemistry, Linkoeping University, Linkoeping Sweden, S-581 83, Swed.
SO J. Org. Chem. (1998), 63(15), 4898-4906
CODEN: JOCEAH; ISSN: 0022-3263
PB American Chemical Society
DT Journal
LA English
AB A series of acyclic C2-sym. HIV protease inhibitors readily accessible from D-mannitol have been developed. Several of the compds. synthesized showed significant in vitro activity against HIV-1 protease.
IT **211994-23-9P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(**HIV-1 protease inhibitors** based on
acyclic carbohydrates)
IT **211994-22-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(**HIV-1 protease inhibitors** based on
acyclic carbohydrates)

L9 ANSWER 5 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1998:279538 CAPLUS
DN 129:4856
TI Syntheses of HIV-protease inhibitors having a peptide moiety which binds to gp120
AU Asagarasu, Akira; Uchiyama, Taketo; Achiwa, Kazuo
CS Sch. Pharm. Sci., Univ. Shizuoka, Shizuoka, 422, Japan
SO Chem. Pharm. Bull. (1998), 46(4), 697-703
CODEN: CPBTAL; ISSN: 0009-2363
PB Pharmaceutical Society of Japan
DT Journal
LA English
AB Some HIV-protease inhibitor derivs. having an N-carbomethoxycarbonyl-prolyl-phenylalanine benzyl ester (CPF) moiety as a binding site to

gp120 were designed and synthesized. Almost all the compds. bearing CPF on the phenoxyacetyl group showed protease-inhibitory activity. [[2-(N-methoxalyl-L-prolyl-D-phenylalaninamido)phenoxy]acetyl]-L-asparagyl-[(2S,3S)-3-amino-2-hydroxy-4-phenylbutyryl]-N-tert-butyl-L-proline amide and its m-isomer (25b), which have the CPF moiety at the ortho- and meta-positions of the phenoxyacetyl group, resp., had anti-HIV activity, although the others showed only protease-inhibitory activity. These results suggest that 25b binds to gp120 inhibits HIV protease.

IT **139694-65-8P 153290-12-1P 158221-95-5P**
**158221-96-6P 158221-97-7P**
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(syntheses of **HIV-protease inhibitors**
having a peptide moiety which binds to gp120)

IT **158221-98-8P 158221-99-9P 158222-03-8P**
**158341-23-2P 207444-99-3P 207445-04-3P**
**207445-05-4P 207445-06-5P 207445-13-4P**
**207445-14-5P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(syntheses of **HIV-protease inhibitors**
having a peptide moiety which binds to gp120)

IT **141171-72-4P 207444-84-6P 207444-85-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(syntheses of **HIV-protease inhibitors**
having a peptide moiety which binds to gp120)

IT **207444-87-9P 207444-88-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(syntheses of **HIV-protease inhibitors**
having a peptide moiety which binds to gp120)

L9 ANSWER 6 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1998:129660 CAPLUS
DN 128:252451
TI HIV-1 Protease Inhibitors Are Substrates for the MDR1 Multidrug Transporter
AU Lee, Caroline G. L.; Gottesman, Michael M.; Cardarelli, Carol O.; Ramachandra, Muralidhara; Jeang, Kuan-Teh; Ambudkar, Suresh V.; Pastan, Ira; Dey, Saibal
CS Laboratory of Cell Biology, National Cancer Institute, Bethesda, MD, 20892, USA
SO Biochemistry (1998), 37(11), 3594-3601
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
OS CJACS

Searcher : Shears 308-4994

AB The FDA approved HIV-1 protease inhibitors, ritonavir, saquinavir, and indinavir, are very effective in inhibiting HIV-1 replication, but their long-term efficacy is unknown. Since in vivo efficacy depends on access of these drugs to intracellular sites where HIV-1 replicates, we detd. whether these protease inhibitors are recognized by the MDR1 multidrug transporter (P-glycoprotein, or P-gp), thereby reducing their intracellular accumulation. In vitro studies in isolated membrane prepns. from insect cells infected with MDR1-expressing recombinant baculovirus showed that these inhibitors significantly stimulated P-gp-specific ATPase activity and that this stimulation was inhibited by SDZ PSC 833, a potent inhibitor of P-gp. Furthermore, photoaffinity labeling of P-gp with the substrate analog [125I]iodoarylazidoprazosin (IAAP) was inhibited by all three inhibitors. Cell-based approaches to evaluate the ability of these protease inhibitors to compete for transport of known P-gp substrates showed that all three HIV-1 protease inhibitors were capable of inhibiting the transport of some of the known P-gp substrates but their effects were generally weaker than other documented P-gp modulators such as verapamil or cyclosporin A. Inhibition of HIV-1 replication by all three protease inhibitors was reduced but can be restored by MDR1 inhibitors in cells expressing MDR1. These results indicate that the HIV-1 protease inhibitors are substrates of the human multidrug transporter, suggesting that cells in patients that express the MDR1 transporter will be relatively resistant to the anti-viral effects of the HIV-1 protease inhibitors, and that absorption, excretion, and distribution of these inhibitors in the body may be affected by the multidrug transporter.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**HIV-1 protease inhibitors** are substrates for the MDR1 multidrug transporter)

L9 ANSWER 7 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1998:110766 CAPLUS
DN 128:225752
TI Effect of protease inhibitors on nucleoside analog phosphorylation in vitro
AU Hoggard, P. G.; Manion, V.; Barry, M. G.; Back, D. J.
CS Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, L69 3GE, UK
SO Br. J. Clin. Pharmacol. (1998), 45(2), 164-167
CODEN: BCPHBM; ISSN: 0306-5251
PB Blackwell Science Ltd.
DT Journal
LA English
AB Combination antiretroviral therapy for human immunodeficiency virus (HIV) infection now involves both nucleoside analogs and protease

inhibitors. Since intracellular phosphorylation is essential for the activity of all the nucleoside analogs, this study was designed to investigate interactions with protease inhibitors at the intracellular level which may alter antiviral efficacy. PHA-stimulated PBMCs (3.times.106 cell/plate) and U937 cells (4.times.106 cells/plate) were incubated with either radiolabeled zidovudine (ZDV), stavudine (d4T), zalcitabine (ddC), lamivudine (3TC) or didanosine (ddI) in the presence and absence of the protease inhibitors, indinavir, ritonavir, and saquinavir (0.1-10 .mu.M) for 24 h. Cells were extd. overnight prior to anal. by radiometric h.p.l.c. Intracellular phosphates were standardized to pmol per million cells. None of the three protease inhibitors tested had any significant effect on the intracellular phosphorylation of the five nucleoside analogs. It is particularly important to focus on the active triphosphate anabolites and data for control vs. ritonavir (10 .mu.M) incubations in U937 cells were as follows: ZDVTP, 0.19 vs. 0.21 pmol/106 cells (mean .+-. s.d.); d4TTP, 0.30 vs. 0.27; 3TCTP, 0.32 vs. 0.26; ddCTP, 0.07 vs. 0.06; ddATP, 0.014 vs. 0.018 pmol/106 cells. The protease inhibitors, indinavir, ritonavir and saquinavir have no effect on the enzymes responsible for phosphorylation. Combining protease inhibitors and nucleoside analogs should not lead to any intracellular interactions in vivo.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(effect of **HIV protease inhibitors** on nucleoside analog phosphorylation in vitro)

L9 ANSWER 8 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1998:66719 CAPLUS
DN 128:162539
TI Discovery of Ritonavir, a Potent Inhibitor of HIV Protease with High Oral Bioavailability and Clinical Efficacy
AU Kempf, Dale J.; Sham, Hing L.; Marsh, Kennan C.; Flentge, Charles A.; Betebenner, David; Green, Brian E.; McDonald, Edith; Vasavanonda, Sudthida; Saldivar, Ayda; Wideburg, Norman E.; Kati, Warren M.; Ruiz, Lisa; Zhao, Chen; Fino, LynnMarie; Patterson, Jean; Molla, Akhteruzzaman; Plattner, Jacob J.; Norbeck, Daniel W.
CS Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL, 60064, USA
SO J. Med. Chem. (1998), 41(4), 602-617
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CJACS
AB The structure-activity studies leading to the potent and clin. efficacious HIV protease inhibitor ritonavir are described.

Beginning with the moderately potent and orally bioavailable inhibitor A-80987, systematic investigation of peripheral (P3 and P2') heterocyclic groups designed to decrease the rate of hepatic metab. provided analogs with improved pharmacokinetic properties after oral dosing in rats. Replacement of pyridyl groups with thiazoles provided increased chem. stability toward oxidn. while maintaining sufficient aq. soly. for oral absorption. Optimization of hydrophobic interactions with the HIV protease active site produced ritonavir, with excellent in vitro potency (EC50 = 0.02 .mu.M) and high and sustained plasma concns. after oral administration in 4 species. Details of the discovery and preclin. development of ritonavir are described.

IT **144141-96-8P 144141-97-9P 144142-00-7P**
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**144142-12-1P 144142-20-1P 144142-66-5P**
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**202816-96-4P 202816-97-5P 202816-98-6P**
**202816-99-7P 202817-00-3P 202817-01-4P**
**202817-02-5P 202817-03-6P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(prepn. of **HIV protease inhibitors** with high oral bioavailability and clin. efficacy)

IT **202817-04-7P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of **HIV protease inhibitors** with high oral bioavailability and clin. efficacy)

IT **144163-44-0**
RL: RCT (Reactant)
(prepn. of **HIV protease inhibitors** with high oral bioavailability and clin. efficacy)

IT **144163-26-8P 144164-10-3P 144164-11-4P**
**144186-45-8P 165315-69-5P 165315-78-6P**
**165315-87-7P 165316-37-0P 202817-10-5P**
**202817-12-7P 202817-13-8P 202817-17-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of **HIV protease inhibitors** with high oral bioavailability and clin. efficacy)

L9 ANSWER 9 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1998:37615 CAPLUS
DN 128:200488

TI Determination of ritonavir, a new HIV protease inhibitor, in biological samples using reversed-phase high-performance liquid chromatography
AU Marsh, Kennan C.; Eiden, Erin; McDonald, Edith
CS Pharmaceutical Products Division, Drug Analysis Department, Abbott Laboratories, Abbott Park, IL, 60064, USA
SO J. Chromatogr., B: Biomed. Sci. Appl. (1997), 704(1 + 2), 307-313
CODEN: JCBBEP; ISSN: 0378-4347
PB Elsevier Science B.V.
DT Journal
LA English
AB A simple, accurate and precise HPLC method has been developed for measurement of ritonavir concns. in human plasma. Ritonavir was partitioned from the plasma using liq.-liq. extn. with a mixt. of Et acetate and hexane at neutral pH, with an av. recovery >80%. Following two sequential washings of the reconstituted sample with hexane, chromatog. sepn. was accomplished on a C18 anal. column with a mobile phase contg. acetonitrile, methanol and 0.01 M tetramethylammonium perchlorate in 0.1 aq. trifluoroacetic acid (40:5:55, vol./vol.) with low wavelength UV detection at 205 nm. Std. curves were linear (r2 > 0.9998) over the concn. range 0.01-15 .mu.g/mL with both inter- and intra-day coeffs. of variation typically less than 5. The stability of ritonavir in plasma was excellent, with no evidence of degrdn. after 5 days at room temp. or after 6 mo in a freezer. Decontamination procedures for HIV-pos. plasma samples showed 5.6 and 10.2 degrdn. following heating to 60.degree.C for 30 or 60 min, resp.
IT **155213-67-5**, Ritonavir
RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(detn. of **HIV protease inhibitor** ritonavir in human plasma by HPLC)

L9 ANSWER 10 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1998:15429 CAPLUS
DN 128:175813
TI HIV protease inhibitors, saquinavir, indinavir and ritonavir: inhibition of CYP3A4-mediated metabolism of testosterone and benzoxazinorifamycin, KRM-1648, in human liver microsomes
AU Inaba, T.; Fischer, N. E.; Riddick, D. S.; Stewart, D. J.; Hidaka, T.
CS Faculty of Medicine, Department of Pharmacology, University of Toronto, Toronto M5S1A8, Can.
SO Toxicol. Lett. (1997), 93(2,3), 215-219
CODEN: TOLED5; ISSN: 0378-4274
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
AB The protease inhibitors, ritonavir, indinavir and saquinavir, the most potent anti-HIV drugs developed to date, interact with many

drugs by competing for CYP3A4, an enzyme central to the metab. of a wide variety of compds. Human liver microsomes were used to compare inhibition by these three protease inhibitors. The inhibition was the greatest with ritonavir and indinavir and less potent with saquinavir.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**HIV protease inhibitors**
(saquinavir and indinavir and ritonavir) and inhibition of cytochrome P 450 3A4-mediated metab. of testosterone and benzoxazinorifamycin (KRM-1648) in human liver microsomes)

L9 ANSWER 11 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1997:812173 CAPLUS
DN 128:80027
TI Pediatric formulation for HIV protease inhibitors
IN Ostovic, Drazen; Thompson, Karen C.
PA Merck & Co., Inc., USA; Ostovic, Drazen; Thompson, Karen C.
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9746222 | A1 | 19971211 | WO 97-US9109 | 19970530 |
| | W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| | AU 9731469 | A1 | 19980105 | AU 97-31469 | 19970530 |
| PRAI | US 96-19097 | | 19960603 | | |
| | GB 96-13109 | | 19960621 | | |
| | WO 97-US9109 | | 19970530 | | |

AB Dispersal or suspension of HIV protease inhibitor in glycerol improves palatability and taste for the prepn. of suitable pediatric formulations in the treatment of AIDS, ARC or HIV infection in children and infants. A pharmaceutical suspension contained Crixivan 100, magnasweet 20 g, bubble gum flavor q.s. and glycerol q.s. 1 mL.

IT **127779-20-8 155213-67-5**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pediatric formulation for **HIV protease inhibitors**)

L9 ANSWER 12 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1997:720276 CAPLUS
DN 127:302916
TI Viracept (Nelfinavir Mesylate, AG1343): A Potent, Orally Bioavailable Inhibitor of HIV-1 Protease
AU Kaldor, Stephen W.; Kalish, Vincent J.; Davies, Jay F. ,II; Shetty, Bhasker V.; Fritz, James E.; Appelt, Krzysztof; Burgess, Jeffrey A.; Campanale, Kristina M.; Chirgadze, Nickolay Y.; Clawson, David K.; Dressman, Bruce A.; Hatch, Steven D.; Khalil, Deborah A.; Kosa, Maha B.; Lubbehusen, Penny P.; Muesing, Mark A.; Patick, Amy K.; Reich, Siegfried H.; Su, Kenneth S.; Tatlock, John H.
CS Agouron Pharmaceuticals Inc., San Diego, CA, 92121, USA
SO J. Med. Chem. (1997), 40(24), 3979-3985
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CJACS
AB Using a combination of iterative structure-based design and an anal. of oral pharmacokinetics and antiviral activity, AG1343 (Viracept, nelfinavir mesylate), a nonpeptidic inhibitor of HIV-1 protease, was identified. AG1343 is a potent enzyme inhibitor (Ki = 2 nM) and antiviral agent (HIV-1 ED50 = 14 nM). An X-ray cocrystal structure of the enzyme-AG1343 complex reveals how the novel thiophenyl ether and phenol-amide substituents of the inhibitor interact with the S1 and S2 subsites of HIV-1 protease, resp. In vivo studies indicate that AG1343 is well absorbed orally in a variety of species and possesses favorable pharmacokinetic properties in humans. AG1343 (Viracept) has recently been approved for marketing for the treatment of AIDS.
IT **169104-89-6P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of and **HIV-1 protease inhibition** by viracept and analogs)
IT **136522-17-3P 168898-57-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of and **HIV-1 protease inhibition** by viracept and analogs)

L9 ANSWER 13 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1997:438126 CAPLUS
DN 127:117088
TI Antagonism between human immunodeficiency virus type 1 protease inhibitors indinavir and saquinavir in vitro
AU Merrill, Debra P.; Manion, Douglas J.; Chou, Ting-Chao; Hirsch, Martin S.

CS Infectious Disease Unit, Harvard Medical School, Massachusetts General Hospital, Boston, MA, 02114, USA
SO J. Infect. Dis. (1997), 176(1), 265-268
CODEN: JIDIAQ; ISSN: 0022-1899
PB University of Chicago Press
DT Journal
LA English
AB Human immunodeficiency virus type 1 (HIV-1) protease inhibitors are a promising class of antiretroviral agents that compromise enzymic function through substrate mimicry. The in vitro susceptibility of a panel of HIV-1 clin. isolates demonstrating various drug resistance phenotypes to combinations of the HIV-1 protease inhibitors saquinavir and indinavir was detd. Antiviral effect was assessed by an HIV-1 p24 antigen redn. assay in phytohemagglutinin-stimulated peripheral blood mononuclear cells after harvesting of cell-free supernatant fluids at peak antigen prodn. (days 4-7). Drug interactions were detd. by median-dose-effect anal., with the combination index (CI) calcd. at several inhibitory concns. (IC50, IC75, IC90, IC95, IC99). The interactive effects ranged from synergy at low efficacy doses to antagonism at higher doses against a pan-susceptible clin. isolate of HIV-1. Against a zidovudine-resistant isolate as well as a multidrug-resistant isolate, the combination of saquinavir and indinavir demonstrated antagonism at all doses.
IT **127779-20-8**, Saquinavir
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antagonism between **HIV**-1 **protease inhibitors** indinavir and saquinavir in vitro)

L9 ANSWER 14 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1997:337741 CAPLUS
DN 127:12782
TI Human immunodeficiency virus type 1 protease inhibitors
AU Mcdonald, Cheryl K.; Kuritzkes, Daniel R.
CS Division of Infectious Diseases, University of Colorado Health Sciences Center, Denver, USA
SO Arch. Intern. Med. (1997), 157(9), 951-959
CODEN: AIMDAP; ISSN: 0003-9926
PB American Medical Association
DT Journal; General Review
LA English
AB A review with 86 refs. Until recently, treatment for human immunodeficiency virus type 1 (HIV-1) infection was limited to the use of nucleoside inhibitors of the viral enzyme reverse transcriptase. While these agents initially offered promise, they have only modest antiviral activity and the benefits of treatment are limited by the emergence of drug resistance and dose-limiting toxic effects.1,2 Development of more potent drugs that target

different stages of the virus life cycle has thus been aggressively pursued. Efforts to develop inhibitors of HIV-1 protease have yielded a potent new class of compds. that suppress HIV-1 replication to an extent far greater than was previously attainable. Four protease inhibitors, saquinavir mesylate, ritonavir, nelfinavir, and indinavir sulfate, have been approved by the Food and Drug Administration. Other agents are undergoing active investigation. The purpose of this article is to review the currently available data on those agents that have been approved for clin. use.

IT **149845-06-7**, Saquinavir mesylate **155213-67-5**, Ritonavir
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**HIV-1 protease inhibitors** design and antiviral activity)

L9 ANSWER 15 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1997:283408 CAPLUS
DN 127:12922
TI Metabolism and disposition of the HIV-1 protease inhibitor ritonavir (ABT-538)in rats, dogs, and humans
AU Denissen, Jon F.; Grabowski, Brian A.; Johnson, Marianne K.; Buko, Alex M.; Kempf, Dale J.; Thomas, Samuel B.; Surber, Bruce W.
CS Abbott Lab., Abbott Park, IL, 60064, USA
SO Drug Metab. Dispos. (1997), 25(4), 489-501
CODEN: DMDSAI; ISSN: 0090-9556
PB Williams & Wilkins
DT Journal
LA English
AB The metab. and disposition of [14C]ritonavir (ABT-538, NOR-VIR), a potent, orally active HIV-1 protease inhibitor, were investigated in male and female Sprague-Dawley rats, beagle dogs, and HIV-neg. male human volunteers. Rats and dogs received a 5 mg/kg i.v., 20 mg/kg oral or 20 mg/kg intraduodenal dose, whereas humans received a single 600-mg liq. oral dose. Ritonavir was cleared primarily via hepatobiliary elimination in all three species. After i.v. or oral dosing in either rats or dogs, >92% of the dose was recovered in rat and dog feces and .ltoreq.4% was recovered in the urine. Humans excreted 86.3% of the oral dose in feces and 11.3% in urine over 6 days. Bile-exteriorized rats and dogs excreted 85.5% and 39.8%, resp., of the i.v. dose in bile, with <3% recovered in urine. Radio-HPLC anal. of bile, feces, and urine from all three species indicated extensive metab. of ritonavir to a no. of oxidative metabolites, some being species-specific, and all involving metab. at the terminal functional groups of the mol. Glucuronide metabolites were obsd. in dog only. Plasma radioactivity consisted predominantly of unchanged parent drug in all three species. M-2,

the product of hydroxylation at the methine carbon of the terminal iso-Pr moiety of ritonavir, was the only metabolite present in human plasma and made up 30.4% of the total dose recovered in human excreta over 6 days. Tissue distribution of ritonavir in rat was widespread, with good distribution into lymphatic tissue but low CNS penetration. Plasma protein binding of ritonavir was high (96-99.5%) in all species and was nonsaturable in humans at concns. up to 30 .mu.g/mL. Partitioning into the formed elements of whole blood was minimal.

IT **155213-67-5**, Ritonavir
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**HIV-1 protease inhibitor** ritonavir
(ABT-538) metab. and disposition in rats, dogs, and humans)

IT **176655-56-4 190649-39-9**
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(**HIV-1 protease inhibitor** ritonavir
(ABT-538) metab. and disposition in rats, dogs, and humans)

IT **176655-55-3 176655-57-5 190649-37-7**
**190649-38-8 190649-40-2**
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**HIV-1 protease inhibitor** ritonavir
(ABT-538) metab. and disposition in rats, dogs, and humans)

L9 ANSWER 16 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1997:219835 CAPLUS
DN 126:301429
TI Lack of stereospecificity in the binding of the P2 amino acid of ritonavir to HIV protease
AU Kempf, Dale J.; Molla, Akhteruzzaman; Marsh, Kennan C.; Park, Chang; Rodrigues, A. David; Komeyeva, Marina; Vasavanonda, Sudthida; Mcdonald, Edith; Flentge, Charles A.; et al.
CS Abbott Laboratories, D-47D, AP9A, Abbott Park, IL, 60064, USA
SO Bioorg. Med. Chem. Lett. (1997), 7(6), 699-704
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier
DT Journal
LA English
AB The biol. and pharmacokinetic properties of the HIV protease inhibitor ritonavir and its D-valinyl diastereomer, A-117673, were found to be indistinguishable. The X-ray crystal structure of the A-117673/HIV protease complex demonstrated similar binding modes for the two inhibitors, with a ca 1 .ANG. difference in the backbone that allows the valine side chain of both compds. to project into the S2 subsite of the enzyme.

IT **155213-67-5**, Ritonavir **183388-65-0**, A 117673
RL: BAC (Biological activity or effector, except adverse); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)
(**HIV protease inhibitor** ritonavir
and diastereomer antiviral and pharmacokinetic properties)

L9 ANSWER 17 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1997:208119 CAPLUS
DN 126:293367
TI Substituted cyclic carbonyls and derivatives thereof useful as retroviral protease inhibitors
IN Lam, Patrick Y.; Jadhav, Prabhakar K.; Eyermann, Charles J.; Hodge, Carl N.; De Lucca, George V.; Rodgers, James D.
PA The Du Pont Merck Pharmaceutical Company, USA
SO U.S., 198 pp. Cont.-in-part of U.S. Ser. No. 47,330, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 5

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | US 5610294 | A | 19970311 | US 94-197630 | 19940216 |
| | EP 765873 | A1 | 19970402 | EP 96-118182 | 19921013 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, SE | | | | |
| | LV 10096 | B | 19950420 | LV 93-341 | 19930514 |
| | WO 9419329 | A1 | 19940901 | WO 94-US1609 | 19940223 |
| | W: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, SK | | | | |
| | RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| | CA 2156594 | AA | 19940901 | CA 94-2156594 | 19940223 |
| | AU 9465493 | A1 | 19940914 | AU 94-65493 | 19940223 |
| | EP 686151 | A1 | 19951213 | EP 94-913262 | 19940223 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| | JP 08509700 | T2 | 19961015 | JP 94-519072 | 19940223 |
| | EP 858999 | A1 | 19980819 | EP 98-106311 | 19940223 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE | | | | |
| | ZA 9401325 | A | 19950825 | ZA 94-1325 | 19940225 |
| | US 5506355 | A | 19960409 | US 94-269281 | 19940630 |
| | US 5559252 | A | 19960924 | US 94-268609 | 19940630 |
| | AU 9532895 | A1 | 19960523 | AU 95-32895 | 19950926 |
| | US 5811422 | A | 19980922 | US 96-770546 | 19961122 |
| PRAI | US 91-776491 | 19911011 | | | |
| | US 92-883944 | 19920515 | | | |
| | US 92-953272 | 19920930 | | | |
| | US 93-23439 | 19930226 | | | |
| | US 93-47330 | 19930415 | | | |
| | EP 92-922262 | 19921013 | | | |
| | US 94-197630 | 19940216 | | | |

EP 94-913262 19940223
WO 94-US1609 19940223
OS MARPAT 126:293367
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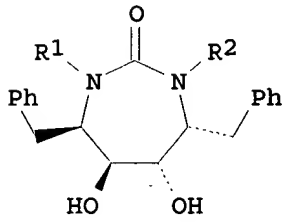


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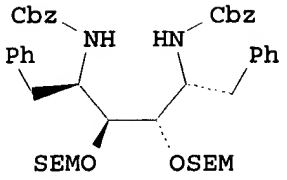


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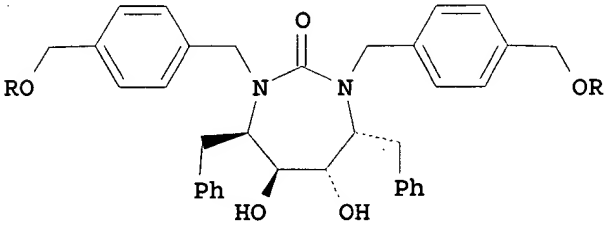


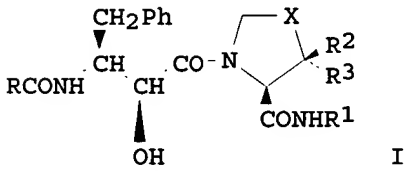

III

AB The invention relates to substituted cyclic carbonyl compds. and derivs., and particularly to cyclic urea derivs. such as I [R1, R2 = H, alkyl, allyl, cyclopropylmethyl, (un)substituted benzyl, etc.]. The compds. are retroviral protease inhibitors, useful in pharmaceutical compns. and methods for treating viral infection. They include prodrugs which have improved aq. soly. and oral bioavailability. For instance, the protected diamine-diol II [Cbz = CO2CH2Ph, SEM = CH2OCH2CH2SiMe3] was N-deprotected by hydrogenolysis (99%), then cyclized with carbonyldiimidazole in CH2Cl2 (93%) to give a cyclic urea intermediate. N,N'-Dialkylation of this using NaH in DMF and alkyl bromides, followed by acid hydrolysis using HCl in MeOH-dioxane gave a variety of I, e.g., compd. III [R = H] (IV). Protection of IV as the acetonide (90%) and esterification with excess N,N-dimethylglycine using EDCI (73%) gave the prodrug III.2HCl [R = COCH2NMe2] (V). In the HIV-1 protease transgenic mouse model, as measured by delay of cataract onset, IV gave a delay of 5 days past control at 100 mg/kg i.p. bid, and 45 days at 400 mg/kg i.p. bid. However, solid IV had only low oral bioavailability, and still only 5% at 40 mg/kg when administered in glycol excipient. In contrast, the prodrug V gave 12% mean bioavailability of IV at only 8 mg/kg orally without excipient.

L9 ANSWER 18 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1997:132760 CAPLUS
DN 126:144550
TI HIV-protease inhibitors
IN Kato, Ryohei; Mimoto, Tsutomu; Fukazawa, Tominaga; Morohashi, Naoko; Kiso, Yoshiaki
PA Japan Energy Corporation, Japan
SO Eur. Pat. Appl., 34 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI EP 751145 | A2 | 19970102 | EP 96-304764 | 19960628 |
| EP 751145 | A3 | 19971008 | | |
| R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| CA 2179935 | AA | 19961231 | CA 96-2179935 | 19960626 |
| JP 10025242 | A2 | 19980127 | JP 96-185631 | 19960626 |
| NO 9602748 | A | 19970102 | NO 96-2748 | 19960628 |
| AU 9656285 | A1 | 19970206 | AU 96-56285 | 19960628 |
| PRAI JP 95-188151 | 19950630 | | | |
| JP 96-140678 | 19960510 | | | |

OS MARPAT 126:144550
GI




I

AB Dipeptides I (X = CH2, CHCl, O, S, SO2; R = 5- or 6-membered monocyclic hydrocarbon or heterocyclic group; R1 = alkyl, monocyclic hydrocarbon group; R2, R3 = H, alkyl) were prepd. as HIV-protease inhibitors. Thus, treatment of a suspension of (R)-[(2S,3S)-3-amino-2-hydroxy-4-phenylbutanoyl]-1,3-thiazolidine-4-N'-tert-butylcarboxamide, (2S,3S)-H-AHPBA-Thz-NH-tBu, and benzoic acid in DMF with EDC.HCl and HOBt-H2O for 14 h at room temp. afforded benzoyl deriv. I (X = S, R = Ph, R1 = t-Bu, R2 = R3 = H). The latter compd. showed 52.0 % HIV protease inhibitor activity at a concn. of 5 .mu.M.
IT **183107-57-5P 183107-74-6P 186537-87-1P 186538-03-4P**

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of **HIV-protease inhibitors**)

IT **153380-43-9 177355-09-8**
RL: RCT (Reactant)
(prepn. of **HIV-protease inhibitors**)

L9 ANSWER 19 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1996:693956 CAPLUS
DN 126:139294
TI HIV-Protease inhibitors. A new class of substances in antiretroviral therapy
AU Mauss, S.; Seidlitz, B.; Jablonowski, H.; Haeussinger, D.
CS Klinik Gastroenterologie Hepatologie Infektiologie, Univ. Duesseldorf, Duesseldorf, D-40225, Germany
SO Dtsch. Med. Wochenschr. (1996), 121(44), 1369-1374
CODEN: DMWOAX; ISSN: 0012-0472
PB Thieme
DT Journal; General Review
LA German
AB A review with 33 refs. on the HIV-protease inhibitors saquinavir, ritonavir, and indinavir.
IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**HIV protease inhibitors** in antiretroviral therapy)

L9 ANSWER 20 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1996:657059 CAPLUS
DN 125:329477
TI Process for the preparation of HIV protease inhibiting peptide analogs.
IN Tien, Jien-heh J.; Menzia, Jerome A.; Cooper, Arthur J.
PA Abbott Laboratories, USA
SO U.S., 7 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI US 5567823 | A | 19961022 | US 95-469965 | 19950606 |
| WO 9639398 | A1 | 19961212 | WO 96-US6812 | 19960513 |
| W: CA, JP, MX | | | | |
| RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| CA 2219983 | AA | 19961212 | CA 96-2219983 | 19960513 |
| EP 830353 | A1 | 19980325 | EP 96-915755 | 19960513 |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI

PRAI US 95-469965 19950606
WO 96-US6812 19960513

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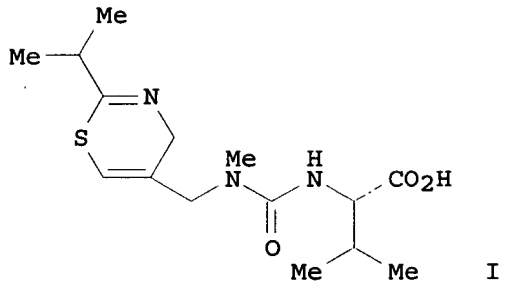

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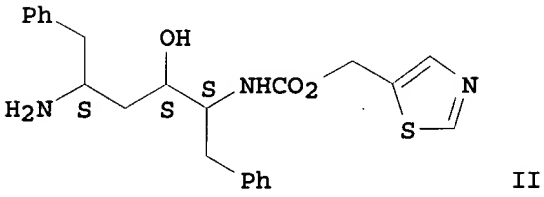

II

AB (2S,3S,5S)-5-[N-[N-[[N-methyl-N-[(2-isopropyl-4-thiazolyl)methyl]amino]carbonyl]-(D- and L-)valinyl]amino]-2-[N-[(5-thiazolyl)methoxycarbonyl]amino]-1,6-diphenyl-3-hydroxyhexane were prepd. without isolation of intermediates by (I) conversion of D- or L-I to a mixed anhydride, (2) conversion of the mixed anhydride to an active ester, and (3) coupling of the active ester with amine (II).

IT **155213-67-5P 183388-65-0P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of **HIV protease inhibiting** peptide analogs)

IT **183388-64-9**
RL: RCT (Reactant)
(prepn. of **HIV protease inhibiting** peptide analogs)

IT **144164-11-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of **HIV protease inhibiting** peptide analogs)

L9 ANSWER 21 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1996:452798 CAPLUS
DN 125:168034
TI Method for preparing HIV-protease-inhibiting N-monosubstituted and N,N'-disubstituted unsymmetrical cyclic ureas via alkylation and dealkylation of intermediate isoureas
IN Rodgers, James D.; Sun, Jung Hui
PA Dupont Merck Pharmaceutical Co., USA
SO U.S., 33 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | US 5532357 | A | 19960702 | US 95-481683 | 19950607 |
| | WO 9640652 | A1 | 19961219 | WO 96-US9021 | 19960606 |
| | W: AM, AT, AU, AZ, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, HU, IL, JP, KG, KR, KZ, LT, LU, LV, MD, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, UA, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| | CA 2223391 | AA | 19961219 | CA 96-2223391 | 19960606 |
| | AU 9659868 | A1 | 19961230 | AU 96-59868 | 19960606 |
| | EP 837855 | A1 | 19980429 | EP 96-917212 | 19960606 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI | | | | |
| | LT 4381 | B | 19980427 | LT 97-188 | 19971203 |
| | NO 9705679 | A | 19980202 | NO 97-5679 | 19971205 |
| | LV 12045 | B | 19980920 | LV 97-248 | 19980128 |
| PRAI | US 95-481683 | | 19950607 | | |
| | WO 96-US9021 | | 19960606 | | |

OS CASREACT 125:168034; MARPAT 125:168034
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A process is claimed for prepn. of title compds. I or pharmaceutically acceptable salts or prodrug forms thereof, wherein: R4 and R7 are the same and are selected from the following groups: C1-C8 alkyl substituted with 0-3 R11; C2-C8 alkenyl substituted with 0-3 R11; C2-C8 alkynyl substituted with 0-3 R11; R11 is independently selected at each occurrence from the group consisting of, e.g., H, keto, halogen, cyano, Ph, benzyl; R22 and R23 are independently selected at each occurrence from the group consisting

of, e.g., C1-C8 alkyl substituted with 0-3 R31; C2-C8 alkenyl substituted with 0-3 R31; C2-C8 alkynyl substituted with 0-3 R31; R31 is independently selected at each occurrence from, e.g., OH, C1-C4 alkoxy, keto, halo, cyano, benzyl; and all functional groups that are reactive with the chem. of this process are protected in such a form that the protecting groups may be kept or removed. This process comprises the steps of (1) contacting isourea II wherein: R1 is Me or Et; R5 and R6 are the same and are selected from, e.g., C1-C6 alkyl substituted with 0-3 R11; C3-C6 alkoxyalkyl substituted with 0-3 R11; C1-C6 alkylcarbonyl substituted with 0-3 R11; R5 and R6 may also be taken together along with the oxygen atoms to which they are attached to form a cyclic acetal group, in an aprotic solvent with at least one molar equivalent of a nitrogen alkylating agent R23-Z, wherein Z is leaving group such as halide or sulfonate and R23 is as defined above, for a period of time sufficient to form cyclic urea III which is optionally isolated; and step (2) contacting III with a reagent or condition or combination of reagents and/or conditions for a period of time sufficient to effect the removal of R5, R6 and any protecting groups and/or to convert functional groups to their desired form to form I which is isolated. Alternatively, monoalkylated isourea II is dealkylated and deprotected to provide monosubstituted urea IV. Thus, e.g., methylation of cyclic urea V with Me triflate afforded isourea VI (75%); alkylation of VI with 3-cyano-4-fluorobenzyl bromide (NaH/DMF) afforded monosubstituted isourea VII (92%); benzylation of VII with PhCH2Br in MeCN afforded disubstituted urea VIII (95%); heterocyclization of VIII with hydrazine afforded the corresponding R23 = 3-aminoindazol-5-ylmethyl acetonide deriv. (100%) which was subsequently deprotected in HCl/THF to provide the diol.

IT **153223-10-0**
RL: RCT (Reactant)
(method for prepg. **HIV-protease-inhibiting** N-monosubstituted and N,N'-disubstituted unsym. cyclic ureas via alkylation of intermediate isoureas)

L9 ANSWER 22 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1996:357017 CAPLUS
DN 125:26233
TI HIV protease inhibitor combination, and therapeutic use
IN Deutsch, Paul J.; Emini, Emilio A.; Vacca, Joseph P.
PA Merck and Co., Inc., USA
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9604913 | A1 | 19960222 | WO 95-US9956 | 19950807 |

Searcher : Shears 308-4994

W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, UZ
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

| | | | | | |
|---|---|---|---|---|---|
| CA | 2197207 | AA | 19960222 | CA 95-2197207 | 19950807 |
| AU | 9533611 | A1 | 19960307 | AU 95-33611 | 19950807 |
| AU | 698664 | B2 | 19981105 | | |
| EP | 774969 | A1 | 19970528 | EP 95-930118 | 19950807 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| CN | 1160350 | A | 19970924 | CN 95-195548 | 19950807 |
| HU | 76540 | A2 | 19970929 | HU 97-402 | 19950807 |
| JP | 10504036 | T2 | 19980414 | JP 95-507422 | 19950807 |
| ZA | 9506662 | A | 19960325 | ZA 95-6662 | 19950810 |
| FI | 9700565 | A | 19970210 | FI 97-565 | 19970210 |
| NO | 9700632 | A | 19970410 | NO 97-632 | 19970211 |

PRAI US 94-289474 19940811
US 94-339369 19941114
US 95-492461 19950720
WO 95-US9956 19950807

AB The combination of the HIV protease inhibitor N-[2(R)-hydroxy-1(S)-indanyl]-2(R)phenylmethyl-4(S)-hydroxy-5-[1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarbamoyl)piperazinyl)]pentaneamide and any one or more of four other potent HIV protease inhibitors is useful in the inhibition of HIV protease, the prevention or treatment of infection by HIV and the treatment of AIDS, either as compds., pharmaceutically acceptable salts, pharmaceutical compn. ingredients, whether or not in combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of treating AIDS and methods of preventing or treating infection by HIV are also described.

IT **127779-20-8 155213-67-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**HIV protease inhibitor** combination, and therapeutic use)

L9 ANSWER 23 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1996:228484 CAPLUS
DN 124:290277
TI HIV protease inhibitor combinations.
IN Barrish, Joel C.; Colonno, Richard J.; Lin, Pin-Fang M.
PA Bristol-Myers Squibb Co., USA
SO Eur. Pat. Appl., 29 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 3

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | EP 691345 | A2 | 19960110 | EP 95-304718 | 19950705 |
| | EP 691345 | A3 | 19960228 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| | US 1649 | H1 | 19970506 | US 95-436868 | 19950517 |
| | AU 9524800 | A1 | 19960118 | AU 95-24800 | 19950704 |
| PRAI | US 94-270614 | 19940705 | | | |
| | US 95-436868 | 19950517 | | | |
| | US 87-79978 | 19870731 | | | |

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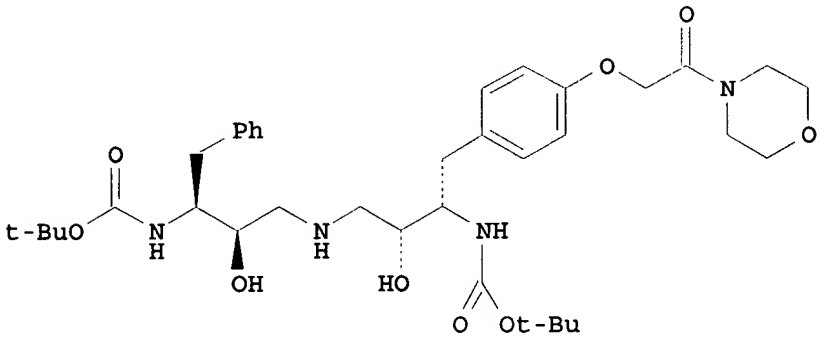
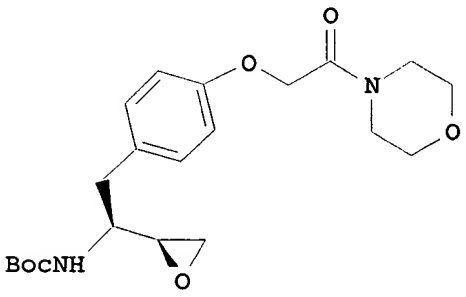
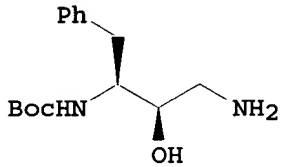


I



II



III

AB A product comprising HIV-1 protease inhibitor (I) (BMS-186318) and .gtoreq.1 of RO 31-8959, SC-52151, A-77003, A-80987, ABT-538, L-735,524, and AG-1343 is claimed. The combinations may eliminate or substantially reduce viral cross-resistance seen with use of individual HIV-1 protease inhibitors. A synthesis of I via coupling of epoxide (II) with aminoalc. (III) is given.

IT **127779-20-8**, RO 31-8959 **134878-17-4**, A-77003
**144141-97-9**, A 80987 **155213-67-5**, ABT-538
RL: BAC (Biological activity or effector, except adverse); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)
(**HIV protease inhibitor** combinations)

L9 ANSWER 24 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1996:222223 CAPLUS
DN 125:25473
TI Saquinavir. A new drug against HIV
AU Strohmaier, Birgit
CS Passau, Germany
SO Pharm. Ztg. (1996), 141(14), 45-6
CODEN: PHZIAP; ISSN: 0031-7136
DT Journal; General Review
LA German
AB A review without refs., describing the structure, resistance development, and pharmacokinetics of the protease inhibitor saquinavir (I), and combination treatment of HIV-infected patients with zidovudine, zalcitabine, and I.
IT **127779-20-8**, Saquinavir
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saquinavir as **HIV-protease inhibitor**)

L9 ANSWER 25 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1996:148284 CAPLUS
DN 124:219422
TI A Possible Involvement of Solvent-Induced Interactions in Drug Design
AU Wang, Hongwu; Ben-Naim, Arieh
CS Department of Physical Chemistry, Hebrew University of Jerusalem, Jerusalem, 91904, Israel
SO J. Med. Chem. (1996), 39(7), 1531-9
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CJACS
AB We propose to study a new factor in designing new drugs. Most approaches to the drug design problem focus on the direct interactions between the drug and the corresponding target. We propose to study specific solvent-induced effects that can contribute to the binding Gibbs energy between the drug and its target. We est. that these indirect effects will contribute significantly to the binding affinity and hopefully improve the clin. efficiency of the drugs.
IT **144141-70-8**, A78791
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**HIV-1 protease inhibitor**;

involvement of solvent-induced interactions in drug design)

L9 ANSWER 26 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1996:129437 CAPLUS
DN 124:219526
TI Resistance of human immunodeficiency virus type 1 to protease inhibitors: selection of resistance mutations in the presence and absence of the drug
AU Borman, Andrew M.; Paulous, Sylvie; Clavel, Francois
CS Unite d'Oncologie Virale CNRS URA 1157, Inst. Pasteur, Paris, 75724, Fr.
SO J. Gen. Virol. (1996), 77(3), 419-26
CODEN: JGVIAY; ISSN: 0022-1317
DT Journal
LA English
AB Inhibitors of the human immunodeficiency virus (HIV) protease are a promising class of antiviral agents that dramatically reduce HIV replication both in culture and in infected patients. However, as for many other antiviral compds., long-term efficacy of these agents is impeded by the emergence of virus variants with increased resistance to their inhibitory action, following selection of specific mutations in the protease coding sequence. We have studied HIV-1 variants that emerged at different stages of selection in the presence of the C2-sym. protease inhibitor ABT-77003. The selection of variants was a gradual process during which mutations accumulated at different sites in the protease, generating virus populations with increasing levels of resistance to the drug. The initially selected viruses had a low level of resistance as well as a markedly reduced replicative capacity. Further accumulation of mutations at secondary sites led to an improvement in both drug resistance and replication. In spite of their reduced infectivity, partially selected virus populations did not readily revert to wild-type when serially passaged in drug-free conditions. Instead, even in the absence of drug, secondary mutations identical to those selected in the presence of the inhibitor continued to emerge. These mutations improved both the intrinsic replicative capacity of the virus and its level of resistance to the inhibitor, suggesting that once committed to drug resistance, readaptation and the enzyme to its natural substrate leads to a redn. of its sensitivity to the inhibitor.
IT **134878-17-4**, A77003
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(resistance of **HIV1** to **protease inhibitor** ABT-77003 and selection of resistance mutations in the presence and absence of the drug)

L9 ANSWER 27 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1996:98265 CAPLUS

DN 124:169196
TI The binding energy of HIV-1 protease inhibitor
AU Ka, Jaejin; Park, Sang-Hyun; Kim, Hojing
CS Department of Chemistry, Seoul National University, Seoul, 151-742, S. Korea
SO Bull. Korean Chem. Soc. (1996), 17(1), 19-24
CODEN: BKCSDE; ISSN: 0253-2964
DT Journal
LA English
AB The potential energies of HIV-1 protease, inhibitor, and their complex have been calcd. by mol. mechanics and the "binding energy", defined as the difference between the potential energy of complex and the sum of potential energies of HIV-1 protease and its inhibitor, has been compared to the free energy in inhibition reaction. The trend in these binding energies seems to agree with that in free energies.
IT **132748-20-0**, JG365
RL: PRP (Properties)
(**HIV-1 proteinase inhibitor**;
binding energies of **HIV**-1 protease and synthetic peptide inhibitors)

L9 ANSWER 28 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1996:26723 CAPLUS
DN 124:202216
TI Stereoselective Synthesis of HIV-1 Protease Inhibitor DMP 323
AU Pierce, Michael E.; Harris, Gregory D.; Islam, Qamrul; Radesca, Lilian A.; Storace, Louis; Waltermire, Robert E.; Wat, Ed; Jadhav, Prabhakar K.; Emmett, George C.
CS Chemical Proces R and D Department, DuPont Merck Pharmaceutical Company, Deepwater, NJ, 08023-0999, USA
SO J. Org. Chem. (1996), 61(2), 444-50
CODEN: JOCEAH; ISSN: 0022-3263
DT Journal
LA English
OS CJACS
AB DMP 323, a potent HIV-1 protease inhibitor, has been synthesized by an efficient stereoselective process, amenable to large scale prepns. The core C2 sym. diol was synthesized by a stereoselective pinacol coupling of CBZ protected D-phenylalanine. Judicious selection of protecting groups allowed cyclic urea formation under mild conditions, enhanced the ease of bis-alkylation, and led to intermediates which were easily purified without chromatog. Addnl., a one-pot, high yield process was developed to prep. the alkylating agent, 4-[(triphenylmethoxy)methyl]benzyl chloride from 1,4-benzenedimethanol.
IT **153223-10-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(stereoselective synthesis of **HIV-1 protease**

**inhibitor** DMP 323)

L9 ANSWER 29 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1995:994185 CAPLUS
DN 124:87033
TI Preparation of HIV protease inhibitors and their (aminohydroxyalkyl)piperazine intermediates.
IN Jungheim, Louis Nickolaus; Shepherd, Timothy Alan
PA Lilly, Eli, and Co., USA
SO PCT Int. Appl., 133 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9521164 | A1 | 19950810 | WO 94-US11352 | 19941006 |
| | W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN | | | | |
| | RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| | US 5461154 | A | 19951024 | US 94-190630 | 19940202 |
| | CA 2180860 | AA | 19950810 | CA 94-2180860 | 19941006 |
| | AU 9479304 | A1 | 19950821 | AU 94-79304 | 19941006 |
| | EP 741719 | A1 | 19961113 | EP 94-930064 | 19941006 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| | HU 76285 | A2 | 19970728 | HU 96-2105 | 19941006 |
| | BR 9408530 | A | 19970805 | BR 94-8530 | 19941006 |
| | JP 09509657 | T2 | 19970930 | JP 94-520584 | 19941006 |
| PRAI | US 94-190630 | 19940202 | | | |
| | WO 94-US11352 | 19941006 | | | |

OS MARPAT 124:87033
GI For diagram(s), see printed CA Issue.
AB Intermediates [I; R = alkyl, pyridylmethyl; R1 = aryl, arylthio; R3 = CON(R4)2, Q1, Q2; p = 4, 5; R4 = H, alkyl, hydroxyalkyl; R5, R6 = H, OH, alkyl, alkoxy, hydroxyalkyl], were prepd. by (a) redn. of pyrazines (II) to give piperazines, (b) alkylation of the piperazines to give intermediates (III), (c) alkylation of III with (IV; R11 = protecting group), and (d) optional deprotection. Thus, pyrazine-2-carboxylic acid in DMF/THF was treated with carbonyldiimidazole and then with Me3CNH2 to give 95% pyrazine 2-N-tert-butylcarboxamide. The latter in EtOH was hydrogenated at 60 psi and 40.degree. overnight to give 95% piperazine 2-N-tert-butylcarboxamide. This in H2O/MeCN was treated with K2CO3 and 3-chloromethylpyridine hydrochloride overnight to give 18%

4-(pyrid-3-ylmethyl)piperazine 2-N-tert-butylcarboxamide. Reflux of the latter compd. with [1S-(1R*,1'R*)]-1-[(1'-N-benzyloxycarbonylamino-2'-phenyl)ethyl]oxirane in Me2CHOH gave 26% [2S-(2R*,2S*,3'R*)]-1-[2'-hydroxy-3'-(N-benzyloxycarbonylamino)-4'-phenylbutyl]-4-(pyrid-3''-ylmethyl)piperazine 2-N-tert-butylcarboxamide. [3S-(3R*,8aR*,2'S*,3'S*)]-2-[2'-hydroxy-3'-phenylthiomethyl-4'-aza-5'-(2''-methyl-3''-hydroxyphenyl)pentyl]decahydroisoquinoline 3-N-tert-butylcarboxamide (prepn. given) inhibited HIV-1 protease with a normalized IC50 = 0.25 ng/mL.

IT **168898-46-2P 168898-47-3P 168898-48-4P**
**168898-49-5P 168898-50-8P 168898-52-0P**
**168898-53-1P 168898-54-2P 168898-55-3P**
**168898-56-4P 168898-57-5P 168898-58-6P**
**168898-59-7P 168898-60-0P 168898-61-1P**
**168898-62-2P 168898-63-3P 168898-65-5P**
**168898-66-6P 168898-67-7P 168898-78-0P**
**168898-79-1P 169104-88-5P 169104-89-6P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of **HIV protease inhibitors** and their (aminohydroxyalkyl)piperazine intermediates)

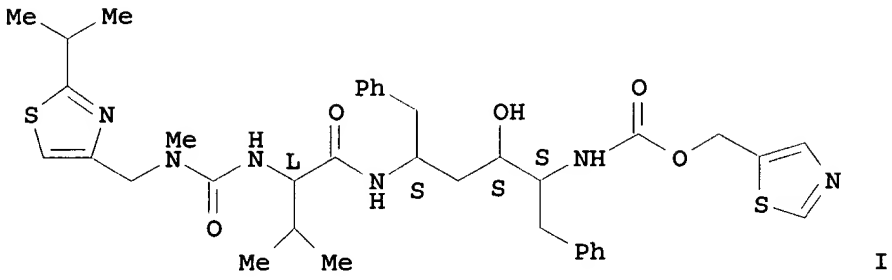
IT **128018-20-2P 128053-39-4P 136522-17-3P**
**137431-05-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of **HIV protease inhibitors** and their (aminohydroxyalkyl)piperazine intermediates)

L9 ANSWER 30 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1995:994162 CAPLUS
DN 124:87790
TI Pharmaceutical compositions containing HIV protease inhibitors and their preparation.
IN Al-Razzak, Laman; Marsh, Kennan C.; Manning, Lourdes P.; Kaul, Dilip
PA Abbott Laboratories, USA
SO PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 9520384 | A1 | 19950803 | WO 95-US232 | 19950103 |
| W: AU, CA, JP, KR, MX | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| CA 2178632 | AA | 19950803 | CA 95-2178632 | 19950103 |
| AU 9515248 | A1 | 19950815 | AU 95-15248 | 19950103 |

| | | | | | |
|---|---|---|---|---|---|
| | EP 732923 | A1 | 19960925 | EP 95-906790 | 19950103 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| | JP 09508383 | T2 | 19970826 | JP 95-520059 | 19950103 |
| | US 5484801 | A | 19960116 | US 95-440277 | 19950512 |
| PRAI | US 94-189021 | 19940128 | | | |
| | US 94-283239 | 19940729 | | | |
| | WO 95-US232 | 19950103 | | | |


GI



I


AB A pharmaceutical compn. which comprises a soln. of an HIV protease inhibiting compd. (e.g., I) in a pharmaceutically acceptable org. solvent comprising a mixt. of (1): (a) a solvent selected from propylene glycol and polyethylene glycol or (b) a solvent selected from polyoxyethyleneglycerol triricinoleate, polyethylene glycol 40 hydrogenated castor oil, fractioned coconut oil, polyoxyethylene 20 sorbitan monooleate and 2-(2-ethoxyethoxy)ethanol or (c) a mixt. thereof; and (2) ethanol or propylene glycol, is claimed. I was prepd. in many steps and its bioavailability in various formulations was studied.


IT **155213-67-5P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pharmaceutical compns. contg. **HIV protease inhibitors** and their prepn.)

IT **143838-10-2P 144164-10-3P**
RL: BYP (Byproduct); PREP (Preparation)
(pharmaceutical compns. contg. **HIV protease inhibitors** and their prepn.)

IT **156732-15-9**
RL: RCT (Reactant)
(pharmaceutical compns. contg. **HIV protease inhibitors** and their prepn.)

IT **137649-69-5P 144141-68-4P 144163-44-0P 144163-85-9P 144164-11-4P 162849-93-6P**

**162849-95-8P 162990-03-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(pharmaceutical compns. contg. **HIV protease inhibitors** and their prepn.)

IT **162990-01-4**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. contg. **HIV protease inhibitors** and their prepn.)

L9 ANSWER 31 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1995:938815 CAPLUS
DN 124:105570
TI Selectivity in the Inhibition of HIV and FIV Protease: Inhibitory and Mechanistic Studies of Pyrrolidine-Containing .alpha.-Keto Amide and Hydroxyethylamine Core Structures
AU Slee, Deborah H.; Laslo, Karen L.; Elder, John H.; Ollmann, Ian R.; Gustchina, Alla; Kervinen, Jukka; Zdanov, Alexander; Wlodawer, Alexander; Wong, Chi-Huey
CS Scripps Research Institute, La Jolla, CA, 92037, USA
SO J. Am. Chem. Soc. (1995), 117(48), 11867-78
CODEN: JACSAT; ISSN: 0002-7863
DT Journal
LA English
OS CJACS
AB This study describes the development of new pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamine core structures as mechanism based inhibitors of the HIV and FIV proteases. The .alpha.-keto amide core structure is approx. 300-fold better than the corresponding hydroxyethylamine isosteric structure and 1300-fold better than the corresponding phosphinic acid deriv. as an inhibitor of the HIV protease. The .alpha.-keto amide is however not hydrated until it is bound to the HIV protease as indicated by the NMR study and the x-ray structural anal. Further anal. of the inhibition activities of hydroxyethylamine isosteres contg. modified pyrrolidine derivs. revealed that a cis-methoxy group at C-4 of the pyrrolidine would improve the binding 5- and 25-fold for the trans-isomer. Of the core structures prepd. as inhibitors of the HIV protease, none show significant inhibitory activity against the mechanistically identical FIV protease, and addnl. complementary groups are needed to improve inhibition.

IT **141197-75-3P**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**HIV** and **FIV proteases inhibition** by pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamines)

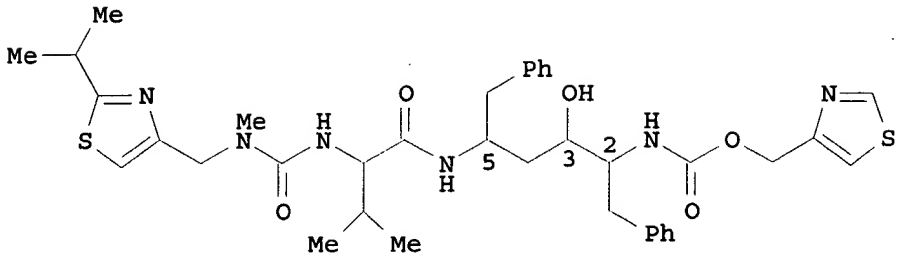
IT **128018-20-2P 172696-14-9P 172696-18-3P**
**172823-16-4P 172823-17-5P 172883-15-7P**

**172953-21-8P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**HIV** and **FIV proteases**
**inhibition** by pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamines)

L9 ANSWER 32 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1995:887807 CAPLUS
DN 123:314522
TI Pharmaceutical composition for HIV protease inhibitor [ritonavir] with improved oral bioavailability
IN Al-razzak, Laman A.; Marsh, Kennan C.; Pyter, Richard A.
PA Abbott Laboratories, USA
SO PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9509614 | A1 | 19950413 | WO 94-US10096 | 19940909 |
| | W: AU, CA, JP, KR | | | | |
| | RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| | US 5559158 | A | 19960924 | US 94-297004 | 19940831 |
| | AU 9477229 | A1 | 19950501 | AU 94-77229 | 19940909 |
| | AU 685509 | B2 | 19980122 | | |
| | EP 721330 | A1 | 19960717 | EP 94-928043 | 19940909 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| | JP 09503501 | T2 | 19970408 | JP 94-510810 | 19940909 |
| PRAI | US 93-130409 | 19931001 | | | |
| | US 94-267273 | 19940628 | | | |
| | US 94-297004 | 19940831 | | | |
| | WO 94-US10096 | 19940909 | | | |

OS MARPAT 123:314522
GI



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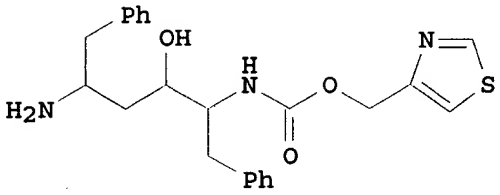


II

AB A solid pharmaceutical compn. is disclosed which comprises a pharmaceutically acceptable adsorbent or mixt. of adsorbents, to which is adsorbed a mixt. of: (1) a pharmaceutically acceptable org. solvent or mixt. of solvents; (2) an HIV protease-inhibiting compd.; and (3) one or more pharmaceutically acceptable acids. The solid compn. can optionally be encapsulated in a hard gelatin capsule. The compn. is particularly applicable to compd. I, and esp. its (2S,3S,5S,L)-isomer [ritonavir; II]. For example, oral administration of unformulated II to dogs gave < 2.0% mean bioavailability. In contrast, 89.6% mean bioavailability was obtained with the following capsule formulation: II 21.84, propylene glycol 10.96, ethanol 22.99, Polysorbate 80 5.31, Cremophor EL 4.4, HCl 1.18, and Cab-o-sil 26.88% by wt. Also described are addnl. oral formulations (comparative and invention), and several syntheses of II. For example, N-(benzyloxycarbonyl)-L-phenylalaninol was converted in 5 steps to (2S,3S,5S)-PhCH2CH(NHZ)CH(OH)CH2CH(NHZ)CH2Ph [Z = benzyloxycarbonyl], which was deprotected and reacted with 5-thiazolylmethyl nitrophenyl carbonate to give intermediate III and its isomer from acylation of the other amino group. Coupling of III with N-[[N-methyl-N-[(2-isopropyl-4-thiazolyl)methyl]amino]carbonyl]-L-valine [prepn. given] using the carbodiimide reagent EDC and 1-hydroxybenzotriazole gave II.

IT **155213-67-5P 162990-01-4P**

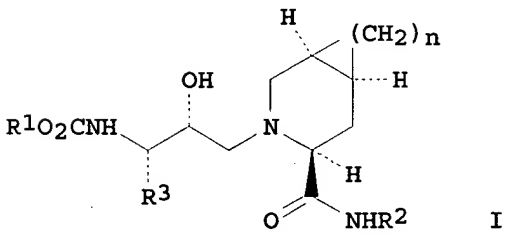
RL: BPR (Biological process); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

(pharmaceutical compn. of **HIV protease inhibitor** with improved oral bioavailability)

L9 ANSWER 33 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1995:784804 CAPLUS
DN 123:198775
TI Preparation of HIV protease inhibitors
IN Ghosh, Arun K.; Thompson, Wayne J.; Mckee, Sean P.
PA Merck and Co., Inc., USA
SO PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9426749 | A1 | 19941124 | WO 94-US5128 | 19940502 |
| | W: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TT, UA, UZ | | | | |
| | RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| | AU 9468288 | A1 | 19941212 | AU 94-68288 | 19940502 |
| PRAI | US 93-61897 | | 19930514 | | |
| | WO 94-US5128 | | 19940502 | | |

OS MARPAT 123:198775
GI




I

AB The title compds. [I; R1 = (un)substituted bicyclic heterocyclic ring; R2 = (un)substituted C1-5 alkyl, (un)substituted carbocyclic; R3 = (un)substituted Ph, (un)substituted cycloalkyl; n = 3, 4] [e.g., (3S,4aS,7aS,2'R,3'S,3"R,3"aS,6"aR) N-tert-Bu octahydro-2-[2'-hydroxy-4'-phenyl-3'-(3"-hexahydrofuro[2,3-b]furanyloxycarbonylamino)butyl]-1H-pyrindene-3-carboxamide], useful in the inhibition of HIV protease (no data), the prevention or treatment of infection by HIV (no data), and the treatment of AIDS (no data), are prepd.

IT **136465-90-2P 136522-17-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of **HIV protease inhibitors**)

IT **156879-13-9P 156928-12-0P 167539-21-1P**
**167539-26-6P 167539-27-7P 167817-13-2P**
**167817-14-3P 167817-15-4P 167817-16-5P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of **HIV protease inhibitors**)

L9 ANSWER 34 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1995:755734 CAPLUS
DN 123:246040
TI Symmetry-based HIV protease inhibitors: rational design of 2-methylbenzamides as novel P2/P2' ligands
AU Randad, Ramnarayan S.; Lubkowska, Lucyna; Bhat, T. Narayana; Munshi, Sanjeev; Gulnik, Sergei V.; Yu, Betty; Erickson, John W.
CS SAIC, Natl. Cancer Inst.-Frederick Cancer Res. and Development Cent., Frederick, MD, 21702, USA
SO Bioorg. Med. Chem. Lett. (1995), 5(15), 1707-12
CODEN: BMCLE8; ISSN: 0960-894X
DT Journal
LA English
AB Readily accessible, non-peptidic, achiral 2-methylbenzamides were designed to serve as P2/P2' ligands for symmetry-based inhibitors of HIV-1 Protease. Introduction of 3-hydroxy substituent provided a potent inhibitor 7 (Ki = 0.8 nM).
IT **168912-67-2P 168912-69-4P**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(symmetry-based **HIV protease inhibitors** in relation to rational design of methylbenzamides as novel P2/P2' ligands)
IT **168912-64-9P 168912-65-0P 168912-66-1P**
**168912-68-3P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(symmetry-based **HIV protease inhibitors** in relation to rational design of methylbenzamides as novel P2/P2' ligands)
IT **168912-63-8**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(symmetry-based **HIV protease inhibitors** in relation to rational design of methylbenzamides as novel P2/P2' ligands)
IT **134878-07-2 144163-44-0**
RL: RCT (Reactant)
(symmetry-based **HIV protease inhibitors** in relation to rational design of

methylbenzamides as novel P2/P2' ligands)

L9 ANSWER 35 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1995:694400 CAPLUS
DN 123:102125
TI Resistance of HIV type 1 to proteinase inhibitor Ro 31-8959
AU Eberle, Josef; Bechowsky, Brigitte; Rose, Dietlinde; Hauser, Ulrike; Helm, Klaus Von Der; Guertler, Lutz; Nitschko, Hans
CS Max von Pettenkofer Institute, University Munich, Munich, D-80336, Germany
SO AIDS Res. Hum. Retroviruses (1995), 11(6), 671-6
CODEN: ARHRE7; ISSN: 0889-2229
DT Journal
LA English
AB During replication of human immunodeficiency virus type 1 (HIV-1), proteolytic cleavage of Gag and Gag-Pol precursor proteins into different functional protein subunits is catalyzed by the viral proteinase, and this enzyme is the target of the antiviral proteinase inhibitor, Ro 31-8959. We investigated in vitro which HIV mutants with reduced sensitivity to Ro 31-8959 emerged during proteinase inhibition treatment; from three different HIV-1 strains, comparable progeny virus resistant to proteinase inhibitor were found, whereas the same exptl. protocol detected no resistant HIV-2 mutants. Mol. anal. of the mutations underlying resistance revealed a multistep mechanism in which an amino acid exchange at position 48 of the proteinase from glycine to valine seemed to play an initial role. This amino acid exchange was common to all resistant isolates, and in all expts. preceded further exchanges at position 90 (leucine to methionine) and/or at position 54 (isoleucine to valine). For wild-type strains the 90% inhibitory concns. of Ro 31-8959 were close to 20 nM, whereas HIV-1 mutants with all 3 amino acid exchanges had more than 50-fold increased 90% inhibitory concns. (above 1000 nM). The primary event (Gly-48 to valine) occurs at the hinge of the flaps of the proteinase, thus hampering entry of the inhibitor to the active center and suggesting steric hindrance. Detailed knowledge of this stereotypic process could open inhibitor design, thus preventing conceivable escape of resistant virus on proteinase inhibitor action.
IT **127779-20-8**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(resistance of **HIV** type 1 to **proteinase inhibitor** Ro 31-8959)

L9 ANSWER 36 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1995:609444 CAPLUS
DN 123:102047
TI HIV protease inhibitor HOE/BAY 793, structure-activity relationships in a series of C2-symmetric diols

AU Budt, Karl-Heinz; Peyman, Anusch; Hansen, Jutta; Knolle, Jochen; Meichsner, Christoph; Paessens, Arno; Ruppert, Dieter; Stowasser, Bernd
CS Hoechst AG, Pharma Res., Frankfurt, 65926, Germany
SO Bioorg. Med. Chem. (1995), 3(5), 559-71
CODEN: BMECEP; ISSN: 0968-0896
DT Journal
LA English
AB A detailed structure-activity relation of C2-sym. diol inhibitors of HIV-1 protease leads to the inhibitor HOE/BAY 793 which is very potent in the inhibition of the enzyme and in the inhibition of viral replication in HIV infected cell culture (IC50: 0.3 nM; EC50: 3 nM). There are well defined steric requirements for the design of the side chains P1-P3 of the inhibitors. In addn., all three side chains need to be lipophilic. While the enzyme tolerates hydrophilic substituents in some cases, drastic redns. in anti-HIV activity are obsd. in cell culture after substitution with hydrophilic groups, which is most likely due to insufficient cell penetration of these compds.
IT **137755-28-3P 165406-33-7P**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**HIV protease inhibitor** HOE/BAY 793
and structure-activity relationships in a series of C2-sym. diol analogs in relation to antiviral activity in human cells)
IT **137755-25-0P 137755-42-1P 137755-47-6P**
**137755-48-7P 137808-03-8P 137808-09-4P**
**137808-16-3P 137821-89-7P 137828-32-1P**
**137828-36-5P 137828-38-7P 137853-70-4P**
**165406-34-8P 165406-35-9P 165406-37-1P**
**165406-39-3P 165406-40-6P 165406-41-7P**
**165406-42-8P 165406-43-9P 165406-44-0P**
**165406-45-1P 165406-46-2P 165406-47-3P**
**165406-48-4P 165406-51-9P 165406-52-0P**
**165876-29-9P 165876-32-4P 165876-34-6P**
**165876-35-7P**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**HIV protease inhibitor** HOE/BAY 793
and structure-activity relationships in a series of C2-sym. diol analogs in relation to antiviral activity in human cells)
IT **129491-63-0 137828-50-3 165876-33-5**
RL: RCT (Reactant)
(**HIV protease inhibitor** HOE/BAY 793
and structure-activity relationships in a series of C2-sym. diol analogs in relation to antiviral activity in human cells)

IT **129491-64-1P 129491-65-2P 134805-49-5P**
**137755-20-5P 137808-10-7P 137808-17-4P**
**137894-61-2P 165406-31-5P 165406-32-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(**HIV protease inhibitor** HOE/BAY 793
and structure-activity relationships in a series of C2-sym. diol analogs in relation to antiviral activity in human cells)

L9 ANSWER 37 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1995:532332 CAPLUS
DN 122:299083
TI Pharmaceutical composition of HIV protease inhibitors
IN Al-Razzak, Laman A.; Marsh, Kennan C.; Manning, Lourdes P.; Kaul, Dilip
PA Abbott Laboratories, USA
SO PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9507696 | A1 | 19950323 | WO 94-US9788 | 19940830 |
| | W: AU, CA, JP, KR | | | | |
| | RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| | CA 2167412 | AA | 19950323 | CA 94-2167412 | 19940830 |
| | AU 9477176 | A1 | 19950403 | AU 94-77176 | 19940830 |
| | AU 695516 | B2 | 19980813 | | |
| | EP 719142 | A1 | 19960703 | EP 94-927973 | 19940830 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| | JP 09502715 | T2 | 19970318 | JP 94-509212 | 19940830 |
| | US 5725878 | A | 19980310 | US 95-435009 | 19950504 |
| PRAI | US 93-120886 | 19930913 | | | |
| | US 94-188511 | 19940128 | | | |
| | US 94-267331 | 19940628 | | | |
| | US 94-288873 | 19940815 | | | |
| | WO 94-US9788 | 19940830 | | | |
| | US 95-402690 | 19950313 | | | |

OS MARPAT 122:299083
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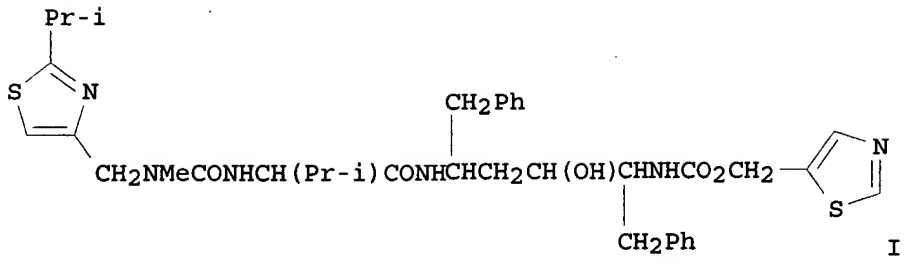


I

AB A pharmaceutical compn. comprising a soln. of an HIV protease-inhibiting compd. in a pharmaceutically acceptable org. solvent comprising an alc., optionally combined with an acid or a combination of acids, shows high oral bioavailability. The soln. can optionally be encapsulated in hard gelatin capsules or soft elastic gelatin capsules, or granulated with a pharmaceutically acceptable granulating agent. Thus, hard gelatin capsules contained HIV protease inhibitor I 8.8, propylene glycol 82.3, EtOH 3.5, HCl 0.9, and water 4.4 wt.%. I was prepd. in multiple steps beginning from N-benzyloxycarbonyl-L-phenylalaninol.

IT **155213-67-5 162990-01-4 162990-02-5**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compn. of **HIV protease inhibitors**)

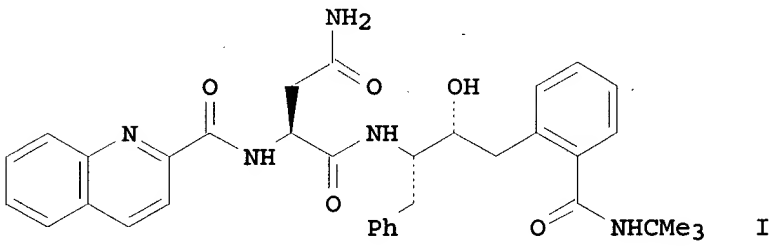
IT **143838-10-2P 144164-10-3P**
RL: BYP (Byproduct); SPN (Synthetic preparation); PREP (Preparation)
(pharmaceutical compn. of **HIV protease inhibitors**)

IT **156732-15-9**
RL: RCT (Reactant)
(pharmaceutical compn. of **HIV protease inhibitors**)

IT **137649-69-5P 144141-68-4P 144163-44-0P 144163-85-9P 144164-11-4P 162849-93-6P 162849-95-8P 162990-03-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(pharmaceutical compn. of **HIV protease inhibitors**)

L9 ANSWER 38 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1995:519323 CAPLUS
DN 122:305873
TI Isophthalic acid derivatives: amino acid surrogates for the inhibition of HIV-1 protease
AU Kaldor, Stephen W.; Dressman, Bruce A.; Hammond, Marlys; Appelt, Krzysztof; Burgess, Jeffrey; Lubbehusen, Penny P.; Muesing, Mark A.;

Hatch, Steven D.; Wiskerchen, Mary Ann; Baxter, Angela J.
CS Lilly Res. Lab., Eli Lilly Co., Indianapolis, 46285, India
SO Bioorg. Med. Chem. Lett. (1995), 5(7), 721-6
CODEN: BMCLE8; ISSN: 0960-894X
DT Journal
LA English
OS CASREACT 122:305873
GI

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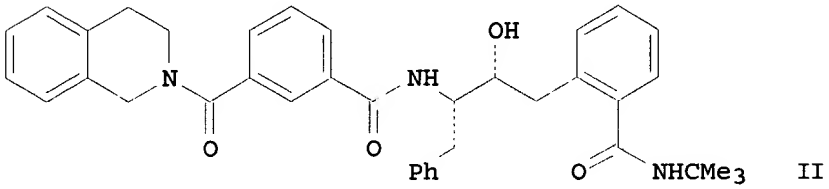



II

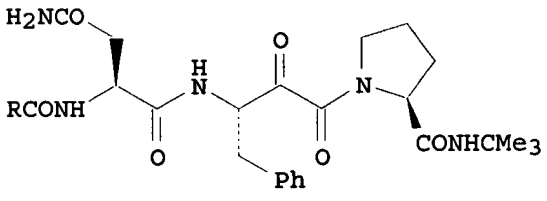
AB Using the x-ray crystal structure of the inhibitor I complexed to HIV-1 protease, a new series of HIV-1 protease inhibitors was developed incorporating substituted isophthalic acid derivs. as amino acid surrogates. Through iterative structure-based design, the lead compd. II was optimized to produce a variety of non-peptide HIV-1 protease inhibitors with significant antiviral activity. In contrast to I, several members of this series exhibit significant oral absorption in animals.

IT **163462-22-4P 163462-23-5P**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**HIV-1 protease inhibitors** contg. isophthalic acid derivs. as amino acid surrogates)

L9 ANSWER 39 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1995:502552 CAPLUS
DN 123:256243
TI Synthesis of a novel C2-symmetrical (2S,5S)-2,5-bis-[(1,1-

dimethylethoxy)carbonylamino]-1,6-diphenylhex-3-ene: applications in the synthesis of potential HIV protease inhibitors
AU Rao, A. V. Rama; Gurjar, Mukund K.; Pal, Shashwati; Pariza, Richard J.; Chorghade, Mukund S.
CS Indian Institute Chemical Technology, Hyderabad, 500 007, India
SO Tetrahedron Lett. (1995), 36(14), 2505-8
CODEN: TELEAY; ISSN: 0040-4039
DT Journal
LA English
OS CASREACT 123:256243
AB The synthesis of a novel and versatile (2S,5S)-2,5-bis[(1,1'-dimethylethoxy)carbonylamino]-1,6-diphenylhex-3-ene (2) based on Julia's olefination strategy coupled with its application in stereoselective prepns. of HIV protease inhibitors has been discussed.
IT **129491-63-0P 129491-64-1P 144141-82-2P 144239-47-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of potential **HIV protease inhibitors**)

L9 ANSWER 40 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1995:440143 CAPLUS
DN 123:112687
TI Synthesis and human immunodeficiency virus (HIV)-1 protease inhibitory activity of tripeptide analogs containing a dioxoethylene moiety
AU Kitazaki, Tomoyuki; Asano, Tsuneo; Kato, Koichi; Kishimoto, Shoji; Itoh, Katsumi
CS Pharmaceutical Research Laboratories III, Takeda Chemical Industries, Ltd., Osaka, 532, Japan
SO Chem. Pharm. Bull. (1994), 42(12), 2636-40
CODEN: CPBTAL; ISSN: 0009-2363
DT Journal
LA English
GI




I

AB Tripeptide analogs I (R = PhCH2O, 2-quinolyl), contg. a dioxoethylene moiety, were designed based on the characteristic

structure of the naturally occurring human immunodeficiency virus (HIV)-1 protease inhibitors RPI-856 A, B, C and D. I showed high inhibitory activity, comparable to that of RPI-856 A, against HIV-1 protease in vitro.

IT **141171-80-4P**
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and **human immunodeficiency virus**-1 **protease inhibitory** activity of tripeptide analogs contg. a dioxoethylene moiety)

IT **141171-73-5P 152843-00-0P 165522-25-8P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and **human immunodeficiency virus**-1 **protease inhibitory** activity of tripeptide analogs contg. a dioxoethylene moiety)

IT **139758-12-6P 141171-72-4P 152886-87-8P**
**153380-43-9P 165522-26-9P 165522-27-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(synthesis and **human immunodeficiency virus**-1 **protease inhibitory** activity of tripeptide analogs contg. a dioxoethylene moiety)

L9 ANSWER 41 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1995:438973 CAPLUS
DN 122:286354
TI Limited sequence diversity of the HIV type 1 protease gene from clinical isolates and in vitro susceptibility to HIV protease inhibitors
AU Winslow, Dean L.; Stack, Sylvia; King, Robert; Scarnati, Helen; Bincsik, Arlene; Otto, Michael J.
CS Du Pont-Merck Pharmaceutical Company, Glenolden, PA, USA
SO AIDS Res. Hum. Retroviruses (1995), 11(1), 107-13
CODEN: ARHRE7; ISSN: 0889-2229
DT Journal
LA English
AB Proviral DNAs from 3 lab. strains and 21 clin. isolates of HIV-1 were extd. from infected cells after proteinase K digestion and the protease gene was PCR amplified and sequenced directly by the Sanger method. In vitro susceptibilities of the virus isolates to protease inhibitors were detd. by the ACTG/DoD consensus assay. Four different HIV protease inhibitors were tested including P9941, a C2 sym. diol (Du Pont-Merck); A80987, an asym. mono-ol (Abbott); XM323, a cyclic urea (Du Pont-Merck); and Ro31-8959, an asym. hydroxyethylene isostere (Roche). Maximum sequence variation was 10% at both the nucleic and amino acid levels. Purine-purine substitutions were most common. Five noncontiguous regions were conserved across all isolates and corresponded to amino acids 1-9

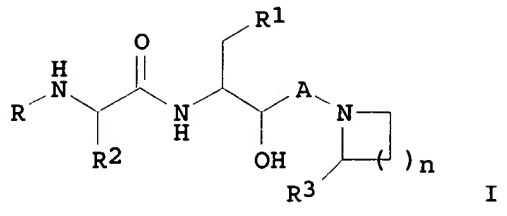
(amino terminal), 21-32 (catalytic site), 47-56 ("flap" region), 78-88 (substrate-binding region), and 94-99 (carboxy terminal). All clin. isolates demonstrated in vitro susceptibility to the protease inhibitors. There was no significant difference between the susceptibility of the ref. strains and the clin. isolates. These data suggest that the variable regions of protease do not contain sites that are important for interactions with the inhibitors tested.

IT **127779-20-8 140196-60-7**, P9941
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(four different **HIV protease inhibitors** were tested including P9941, a C2 sym. diol; A80987, an asym. mono-ol; XM323, a cyclic urea; and Ro31-8959, an asym. hydroxyethylene isostere; all clin. isolates demonstrated in vitro susceptibility)

L9 ANSWER 42 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1995:264545 CAPLUS
DN 122:55900
TI Inhibitors of HIV protease useful for the treatment of AIDS.
IN Jungheim, Louis Nickolaus; Shepherd, Timothy Alan
PA Lilly, Eli, and Co., USA
SO Eur. Pat. Appl., 61 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | EP 604185 | A1 | 19940629 | EP 93-310359 | 19931220 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| | US 5733906 | A | 19980331 | US 93-134329 | 19931012 |
| | ZA 9309475 | A | 19950619 | ZA 93-9475 | 19931217 |
| | NO 9304719 | A | 19940623 | NO 93-4719 | 19931220 |
| | AU 9352528 | A1 | 19940707 | AU 93-52528 | 19931220 |
| | AU 667146 | B2 | 19960307 | | |
| | HU 69693 | A2 | 19950928 | HU 93-3679 | 19931220 |
| | IL 108092 | A1 | 19980615 | IL 93-108092 | 19931220 |
| | CA 2112042 | AA | 19940623 | CA 93-2112042 | 19931221 |
| | FI 9305778 | A | 19940623 | FI 93-5778 | 19931221 |
| | JP 06271534 | A2 | 19940927 | JP 93-322750 | 19931221 |
| | BR 9305162 | A | 19941101 | BR 93-5162 | 19931221 |
| | CN 1094399 | A | 19941102 | CN 93-112962 | 19931221 |
| PRAI | US 92-995256 | 19921222 | | | |
| | US 93-134329 | 19931012 | | | |

OS MARPAT 122:55900
GI



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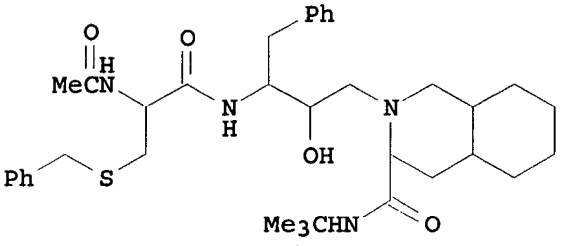


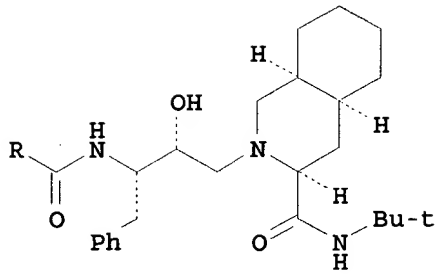
II

AB Oligopeptide analogs I (R1 = aryl, alkyl, alkylthio, etc.; R2 = amino acid side chain, etc.; ) were disclosed. I are HIV protease inhibitors useful for the treatment of HIV infection and AIDS. Claimed example compd., [2R-(2R*,3S*,6S*,4a'S*,8a'S*)]-N-(tert-butyl)-2-[2-hydroxy-3-(phenylmethyl)-4-aza-5-oxo-6-(ethanoylamino)-7-[(phenylmethyl)thio]heptyl]decahydro-3-isoquinolinecarboxamide (II) was prepd.

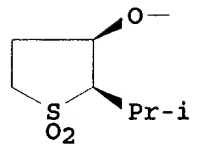
IT **159878-24-7P 159878-25-8P 159878-26-9P 159878-27-0P 159878-28-1P 159878-29-2P 159878-30-5P 159878-31-6P 159991-28-3P 159991-29-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as **HIV protease inhibitor** virucide)

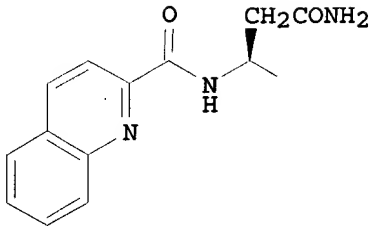
L9 ANSWER 43 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1995:5849 CAPLUS
DN 123:32926
TI The Development of Cyclic Sulfolanes as Novel and High-Affinity P2 Ligands for HIV-1 Protease Inhibitors
AU Ghosh, Arun K.; Lee, Hee Yoon; Thompson, Wayne J.; Culberson, Chris; Holloway, M. Katharine; McKee, Sean P.; Munson, Peter M.; Duong, Tien T.; Smith, Anthony M.; et al.
CS Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA, 19486, USA
SO J. Med. Chem. (1994), 37(8), 1177-88
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal

LA English
OS CJACS
GI



I

$R^1$ = 

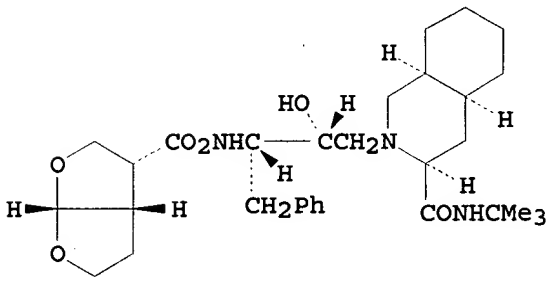
$R^2$ = 

AB Design and synthesis of a novel series of protease inhibitors incorporating conformationally constrained cyclic ligands for the S2-substrate binding site of HIV-1 protease is described. Inhibitor I (R = R1) (IC50 3.5 nM, CIC95 50 .+-. 14 nM) has comparable in vitro antiviral potency to the current clin. candidate I (R = R2) (Ro 31-8959) but of reduced mol. wt. due to the exclusion of the P3 quinoline ligand. Also, it has been demonstrated that octahydropyrindene is an effective replacement for decahydroisoquinoline.

IT **147949-29-9P 147949-30-2P 147949-31-3P**
**147949-32-4P 147949-33-5P 147949-34-6P**
**147949-35-7P 147977-17-1P 147977-18-2P**
**147977-19-3P 147977-20-6P 147977-21-7P**
**147977-22-8P 150330-55-5P 150330-67-9P**
**150406-19-2P 150406-23-8P 161404-82-6P**
**161511-64-4P 162776-43-4P 162776-45-6P**
**162776-47-8P 162776-49-0P 162776-50-3P**
**162870-64-6P 162870-65-7P 162870-66-8P**
**162870-67-9P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and **HIV protease-inhibiting** activity of acylaminobutyldecahydroisoqinolines)

IT **136465-90-2P 136522-17-3P 147949-28-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and **HIV protease-inhibiting** activity of acylaminobutyldecahydroisoqinolines)

L9 ANSWER 44 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1994:621038 CAPLUS
DN 121:221038
TI Structure-Based Design of HIV-1 Protease Inhibitors: Replacement of Two Amides and a 10.pi.-Aromatic System by a Fused Bis-tetrahydrofuran
AU Ghosh, Arun K.; Thompson, Wayne J.; Fitzgerald, Paula M. D.; Culberson, J. Chris; Axel, Melinda G.; McKee, Sean P.; Huff, Joel R.; Anderson, Paul S.
CS Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA, 19486, USA
SO J. Med. Chem. (1994), 37(16), 2506-8
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CJACS
GI




I

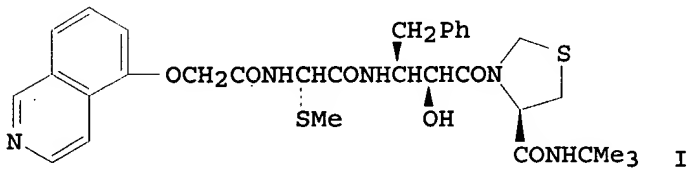
AB The structure-based design of a conformationally constrained fused bistetrahydrofuran effectively replaces 2 amide bonds and a 10.pi.-arom. system of the present clin. candidate, Ro 31-8959. The inhibitor (I) (IC50 = 1.8 nM,; CIC95 = 46 nM) thus obtained, showed comparable in vitro antiviral activities to inhibitors in the hydroxyethylamine class with both P2 and P3 ligands. To obtain information regarding the ligand binding site interactions, a single crystal of the inhibitor I complexed with HIV-1 protease was generated, and the 3-dimensional structure was detd. by x-ray diffraction to 2.10 .ANG. resoln. Interestingly, the oxygen-1 and oxygen-6 of the bis-tetrahydrofuran ligand are within hydrogen bonding distance to the Asp 29 NH and Asp 30 NH present in the S2 binding domain of the HIV-1 protease. The design and synthesis of

such a high affinity ligand led to improved aq. soly. and redn. in mol. wt. due to exclusion of the P3 ligand.

IT **127779-20-8**, Ro 31-8959
RL: BIOL (Biological study)
(**HIV-1 protease inhibitor**, analogs prepn in relation to)

IT **156879-13-9P 156928-12-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as **HIV-1 protease inhibitor**)

L9 ANSWER 45 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1994:499067 CAPLUS
DN 121:99067
TI Structure-activity relationships of tripeptide HIV protease inhibitors containing the hydroxymethylcarbonyl isostere
AU Enomoto, Hiroshi; Mimoto, Tsutomu; Kisanuki, Sumitsugu; Kimura, Tooru; Hattori, Naoko; Kageyama, Seiji; Mitsuya, Hiroaki; Akaji, Kenichi; Kiso, Yoshiaki
CS Dep. Med. Chem., Kyoto Pharm. Univ., Kyoto, 607, Japan
SO Pept. Chem. (1993), 31st, 181-4
CODEN: PECHDP; ISSN: 0388-3698
DT Journal
LA English
GI



I

AB The inhibitors which had substitution of amino acid at P2 and/or P1 position of KNI-272 (I) with more lipophilic or hydrophilic residues were examd. in an enzyme inhibitory assay and antiviral assay. All the compds. inhibited HIV protease as strongly as I, but there was a difference in antiviral activities of those compds. Low antiviral activities were shown by more hydrophilic compds. than I, while more lipophilic ones showed potent activities comparable to I.

IT **138258-64-7**, KNI 93 **139694-65-8**, KNI 102
RL: BIOL (Biological study)
(**HIV-1 protease inhibitor**, structure in relation to)

L9 ANSWER 46 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1994:428001 CAPLUS
DN 121:28001
TI A rapid and simple screening method for HIV-1 protease inhibitors using recombinant Escherichia coli
AU Kaneto, Rei; Kojima, Ikuo; Shibamoto, Norio; Nishida, Hiroshi; Okamato, Rokuro; Akagawa, Hisayoshi; Mizuno, Satoshi
CS Cent. Res. Lab., Mercian Corp., Fujisawa, 251, Japan
SO J. Antibiot. (1994), 47(4), 492-5
CODEN: JANTAJ; ISSN: 0021-8820
DT Journal
LA English
AB This report deals with construction of a recombinant plasmid carrying the chem. synthesized HIV-1 protease gene and its successful expression in Escherichia coli. A screening system for HIV-1 protease inhibitors from microbial metabolite origin was established by using the expressed protease and a peptide analogous to one of the HIV-1 polyproteins. A novel screening system of naturally occurring protease inhibitors was also established by using E. coli carrying the recombined plasmid. A comparison of th 2 screening systems is made and their advantages are discussed.
IT **127779-20-8**
RL: USES (Uses)
(**HIV-1 protease inhibition** by)

L9 ANSWER 47 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1994:289408 CAPLUS
DN 120:289408
TI Three-dimensional QSAR of human immunodeficiency virus (I) protease inhibitors. 1. A CoMFA study employing experimentally-determined alignment rules
AU Waller, Chris L.; Oprea, Tudor I.; Giolitti, Alessandro; Marshall, Garland R.
CS Cent. Mol. Des., Washington Univ., St. Louis, MO, 63130, USA
SO J. Med. Chem. (1993), 36(26), 4152-60
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CJACS
AB Comparative mol. field anal. (CoMFA), a 3-dimensional, quant. structure-activity relationship (QSAR) paradigm, was used to exam. the correlations between the calcd. physicochem. properties and in the vitro activities of a series of human immunodeficiency virus (HIV-1) protease inhibitors. The training set consisted of 59 mols. from five structurally-diverse transition-state isostere classes: hydroxyethylamine, statine, norstatine, keto amide, and dihydroxyethylene. The availability of x-ray crystallog. data for at least one representative from each class bound to the protease provided information regarding not only the active conformation of each ligand but also, via superimposition of protease backbones, the

relative positions of each ligand with respect to one another in the active site of the enzyme. Once aligned, these mols. served as templates on which addnl. congeners were field-fit minimized. Addnl. alignment rules were derived from minimization of the ligands in the active site of the semirigid protease. The predictive ability of each resultant model was evaluated using a test set comprised of mols. contg. a novel transition-state isostere: hydroxyethylurea. Crystallog. studies indicated an unexpected binding mode for this series of compds. which precluded the use of the field-fit minimization alignment technique. The test set mols. were, therefore, subjected to a limited systematic search in conjunction with active-site minimization. The conformer of each mol. expressing the lowest interaction energy with the active site was included in the test set. Field-fit minimization of neutral mols. to crystal ligands and active-site minimizations of protonated ligands yielded predictive correlations for HIV-1 protease inhibitors. The use of crystallog. data in the detn. of alignment rules and field-fit minimization as a mol. alignment tool in the absence of direct exptl. data regarding binding modes is strongly supported by these results.

IT **127749-95-5 127779-20-8 132234-38-9**
**132234-39-0 136522-18-4 137515-64-1**
**137622-86-7 137622-87-8 137693-11-9**
**139694-65-8 139758-12-6 141171-72-4**
**141171-73-5 141171-74-6 141171-76-8**
**141171-77-9 141171-78-0 141171-79-1**
**141171-80-4 141171-81-5 141197-75-3**
**141269-68-3 153126-40-0 153126-41-1**
**153220-54-3 153220-55-4**
RL: BIOL (Biological study)
(**human immunodeficiency virus** 1
**protease inhibition** by, QSAR of)

L9 ANSWER 48 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1994:245776 CAPLUS
DN 120:245776
TI Preparation of cyclic amides of 3-amino-2-hydroxycarboxylic acids as HIV protease inhibitors
IN Krantz, Alexander; Tam, Tim Fat; Castelhano, Arlindo Lucas; Nestor, John Joseph, Jr.
PA Syntex (U.S.A.), Inc., USA
SO PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

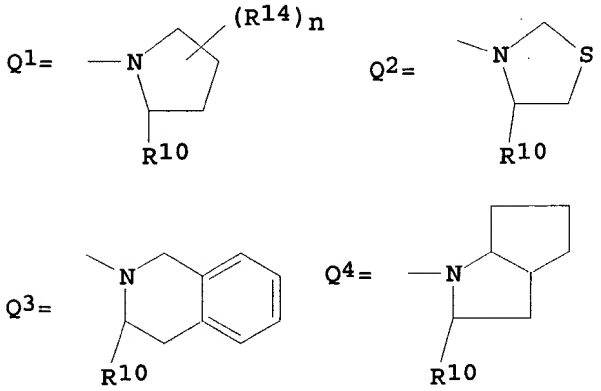
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9313066 | A1 | 19930708 | WO 92-US10772 | 19921218 |

Searcher : Shears 308-4994

W: AU, CA, FI, HU, JP, KR, NO, NZ
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

| | | | | | |
|---|---|---|---|---|---|
| AU 9332782 | A1 | 19930728 | AU 93-32782 | 19921218 |
| ZA 9209869 | A | 19940620 | ZA 92-9869 | 19921218 |

PRAI US 91-812905 19911220
WO 92-US10772 19921218
OS MARPAT 120:245776
GI




AB R1R2NCHR3CONHCHR4CR5R6COR7 [R1 = (ar)alkoxycarbonyl, (substituted) aralkanoyl, aroyl, heterocyclylcarbonyl, aryloxyalkanoyl, carbamoyl, heterocyclyloxyalkanoyl; R2, R5 = H; R3 = (substituted) alkyl, R4 = (substituted) aryl, aralkyl; R6 = OH; R5R6 = O; R1 = Q1-Q4, etc.; n = 0-2; R10 = alkoxycarbonyl, (substituted) carbamoyl; R14 = OH, alkyl, alkoxy, Ph], were prepd. Thus, N'-tert-Bu prolinamide (prepn. given) was coupled with (2S,3S)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoic acid using EDCI/hydroxybenzotriazole in DMF to give 1-[(2S,3S)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-N'-tert-butyl-L-prolinamide. I inhibited HIV protease with IC50 = 0.49-30 nM. I dosage formulations are given.

IT **139694-65-8P 139758-12-6P 141171-73-5P**
**141171-74-6P 141171-76-8P 141171-77-9P**
**141171-78-0P 141171-79-1P 141171-80-4P**
**141171-81-5P 141197-75-3P 143934-35-4P**
**143934-48-9P 144780-35-8P 144830-03-5P**
**153290-07-4P 153290-08-5P 153290-10-9P**
**153290-11-0P 153290-12-1P 153290-13-2P**
**153290-14-3P 153290-15-4P 153290-16-5P**
**153290-17-6P 153290-18-7P 153290-19-8P**
**153290-20-1P 153290-21-2P 153290-22-3P**
**153290-23-4P 153290-24-5P 153290-25-6P**

**153290-26-7P 153290-27-8P 153290-28-9P**
**153290-29-0P 153290-31-4P 153290-32-5P**
**153290-33-6P 153290-34-7P 153290-35-8P**
**153290-36-9P 153290-37-0P 153290-38-1P**
**153290-39-2P 153290-40-5P 153290-41-6P**
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**153290-45-0P 153290-46-1P 153290-47-2P**
**153290-48-3P 153290-49-4P 153290-50-7P**
**153290-51-8P 153290-52-9P 153313-34-9P**
**153380-12-2P 153380-13-3P 153380-14-4P**
**153380-16-6P 153380-17-7P 153380-18-8P**
**153380-19-9P 153380-20-2P 153380-21-3P**
**153380-22-4P 153380-23-5P 153380-24-6P**
**153380-25-7P 153380-26-8P 153380-27-9P**
**153380-28-0P 153380-29-1P 153380-30-4P**
**153380-31-5P 153381-18-1P 153546-68-0P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as **HIV protease inhibitor**
)

L9 ANSWER 49 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1994:208003 CAPLUS
DN 120:208003
TI Characterization of human immunodeficiency virus type 1 variants with increased resistance to a C2-symmetric protease inhibitor
AU Ho, David D.; Toyoshima, Takuo; Mo, Hongmei; Kempf, Dale J.; Norbeck, Daniel; Chen, Chih Ming; Wideburg, Norman E.; Burt, Stan K.; Erickson, John W.; Singh, Mandaleshwar K.
CS Sch. Med., New York Univ., New York, NY, 10016, USA
SO J. Virol. (1994), 68(3), 2016-20
CODEN: JOVIAM; ISSN: 0022-538X
DT Journal
LA English
AB Inhibitors of the human immunodeficiency virus type 1 protease represent a promising class of antiviral drugs for the treatment of AIDS, and several are now in clin. trials. Here, the authors report the in vitro selection of viral variants with decreased sensitivity to a C2-sym. protease inhibitor (A-77003). The authors show that a single amino acid substitution (Arg to Gln or Lys) at position 8 of the protease results in a substantial decrease in the inhibitory activity of the drug on the enzyme and a comparable increase in viral resistance. These findings, when analyzed by using the three-dimensional structure of the protease-drug complex, provide a strategic guide for the future development of inhibitors of the human immunodeficiency virus type 1 protease.
IT **127779-20-8 129491-65-2**, A 76215
**134805-77-9**, A 76889 **134878-16-3**, A 76928
**134878-17-4**, A 77003

RL: BIOL (Biological study)
(**HIV-1 protease inhibitory** activity
of, enzyme structure and resistance to antiviral action in
relation to)

L9 ANSWER 50 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1994:191116 CAPLUS
DN 120:191116
TI Process for the preparation of a substituted diaminodiol
IN Sowin, Thomas J.; Hannick, Steven M.; Doherty, Elizabeth M.; Sato, Takahiro; Suzuki, Takayuki
PA Abbott Laboratories, USA
SO PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 6

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 9323361 | A1 | 19931125 | WO 93-US4403 | 19930510 |
| W: CA, JP | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| PRAI US 92-885575 | | 19920519 | | |

OS MARPAT 120:191116
AB Title compds. (I; PhCH2CH(R3NH)CH(OH)CH(OH)CH(R3NH)CH2Ph) (wherein R3 = H, N-protectant) useful as HIV protease inhibitor (no data), are prepd. L-Phenylalamine Me ester-HCl (prepn. given) in CHCl3 was cooled to 0.degree., Na2CO3 was added followed by ClCO2CH2Ph to give the benzoyloxycarbony deriv., which was treated with LiAlH4 to the alaninol, treated with (COCl)2 to give the alaninal and in turn reacted with VCl3(THF)3 and Zn dust to give a mixt. of diols which were treated with acetone and concd. H2SO4 to give (2S,3R,4R,5S)-I (R3 = PhCH2O2C).
IT **134878-07-2P 134878-17-4P 137649-69-5P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as **HIV protease inhibitor**
)

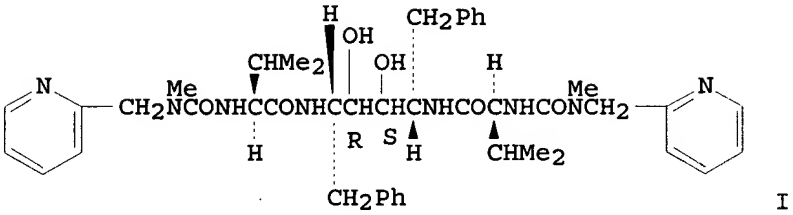
L9 ANSWER 51 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1994:153056 CAPLUS
DN 120:153056
TI Human Immunodeficiency Virus Type 1 Protease Inhibitors: Evaluation of Resistance Engendered by Amino Acid Substitutions in the Enzyme's Substrate Binding Site
AU Sardana, Vinod V.; Schlabach, Abner J.; Graham, Pia; Bush, Bruce L.; Condra, Jon H.; Culberson, J. Chris; Gotlib, Leah; Graham, Donald

J.; Kohl, Nancy E.; et al.
CS Department of Virus and Cell Biology, Merck Research Laboratories, West Point, PA, 19486, USA
SO Biochemistry (1994), 33(8), 2004-10
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
OS CJACS
AB The human immunodeficiency virus type 1 (HIV-1) protease is a homodimeric aspartyl endopeptidase that is required for virus replication. A no. of specific, active-site inhibitors for this enzyme have been described. Many of the inhibitors exhibit significant differences in activity against the HIV-1 and HIV type 2 (HIV-2) enzymes. An initial study was conducted to ascertain the HIV-1 protease's potential to lose sensitivity to several test inhibitors while retaining full enzymic activity. The substrate binding sites of the HIV-1 and HIV-2 enzymes are almost fully conserved, except for four amino acid residues at positions 32, 47, 76, and 82. Accordingly, recombinant mutant type 1 proteases were constructed that contained the cognate type 2 residue at each of these four positions. The substitution at position 32 resulted in a significant adverse effect on inhibitor potency. However, this substitution also mediated a noted decrease in the Km of the substrate. Individual substitutions at the remaining three positions, as well as a combination of all four substitutions, had very little effect on enzyme activity or inhibitor susceptibility. Hence, the four studied active site residues are insufficient to be responsible for differences in inhibitor sensitivity between the HIV-1 and HIV-2 proteases and are unlikely to contribute to the generation of inhibitor-resistant mutant HIV-1 protease.
IT **127779-20-8**, Ro 31-8959
RL: BIOL (Biological study)
(**HIV protease inhibition** by,
resistance to, substitution mutation effect on)

L9 ANSWER 52 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1994:152978 CAPLUS
DN 120:152978
TI Influence of Stereochemistry on Activity and Binding Modes for C2 Symmetry-Based Diol Inhibitors of HIV-1 Protease
AU Hosur, Madhusoodan V.; Bhat, T. Narayana; Kempf, Dale J.; Baldwin, Eric T.; Liu, Beishan; Gulnik, Sergei; Wideburg, Norman E.; Norbeck, Daniel W.; Appelt, Krzysztof; Erickson, John W.
CS Frederick Biomedical Supercomputing Center, PRI/DynCorp, Frederick, MD, 21702, USA
SO J. Am. Chem. Soc. (1994), 116(3), 847-55
CODEN: JACSAT; ISSN: 0002-7863
DT Journal
LA English

OS CJACS

GI



I

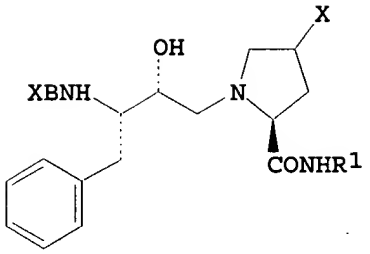
AB The incorporation of C2 symmetry has become a useful paradigm in the design of active site inhibitors for HIV-1 protease (HIV PR) and has led to the design of a series of highly potent, C2 symmetry-based, diol-contg. inhibitors of HIV PR, one of which, A-77003 (I), has reached clin. trials. However, the stereochem. of the diol core influences protease inhibition and antiviral activity in a manner that is not well understood. The authors analyzed the crystal structures of a diastereomeric series of C2 symmetry-based diol inhibitors, along with a deshydroxy analog, bound to HIV PR and found that the stereochem. of the diol core influences the mode of binding to the active site aspartic acids. Diasteromers with similar binding affinity can bind in different, asym. and sym., modes, while those with different binding affinities can bind in a similar manner. The positional symmetry of an inhibitor with respect to the enzyme C2 axis may be distinguished from its conformational symmetry. The structural differences between the inhibitor complexes were mainly confined to the central core portion of the diols, can be described by torsional differences about the central three bonds, and primarily affect interactions within the active site pocket formed by Asp 25/125 and Gly 27/127. Some flexibility in the enzyme backbone at Gly 127 was also apparent. Based on these results, the authors suggest that the binding mode for central hydroxy-bearing, C2-sym. inhibitors will be detd. by how well the inhibitor can simultaneously optimize hydrogen bonding with the active site carboxylate groups and van der Waals contacts with the neighboring backbone atoms of the active site ".psi."-loops. A sym. hydrogen-bonding arrangement with either one or two sym. positioned hydroxy groups appears to be preferred over less sym. configurations.

IT **134805-77-9**, A 76889 **134878-16-3**, A 76928
**134878-17-4**, A 77003 **144141-70-8**, A 78791
RL: BIOL (Biological study)
(**HIV-1 Proteinase inhibition** by,
structure in, antiviral activity relation to)

L9 ANSWER 53 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1994:135132 CAPLUS
DN 120:135132
TI Substituted pyrrolidine derivatives as HIV protease inhibitors
IN Gorys, Vida; Soucy, Francois; Yoakim, Christiane; Beaulieu, Pierre Louis
PA Bio-Mega/Boehringer Ingelheim Research Inc., Can.
SO Eur. Pat. Appl., 26 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | EP 560269 | A1 | 19930915 | EP 93-103713 | 19930309 |
| | EP 560269 | B1 | 19950531 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| | ZA 9301777 | A | 19930923 | ZA 93-1777 | 19930212 |
| | CA 2092653 | AA | 19930914 | CA 93-2092653 | 19930312 |
| | AU 9335165 | A1 | 19930916 | AU 93-35165 | 19930312 |
| | AU 663164 | B2 | 19950928 | | |
| | HU 70147 | A2 | 19950928 | HU 93-729 | 19930312 |
| | PL 173459 | B1 | 19980331 | PL 93-298038 | 19930312 |
| | JP 06025158 | A2 | 19940201 | JP 93-54141 | 19930315 |
| | CN 1096292 | A | 19941214 | CN 93-106800 | 19930608 |
| | US 5552405 | A | 19960903 | US 95-509268 | 19950731 |
| PRAI | US 92-850596 | 19920313 | | | |
| | US 93-25681 | 19930303 | | | |
| | US 94-198237 | 19940218 | | | |
| | US 94-326442 | 19941020 | | | |

OS MARPAT 120:135132
GI

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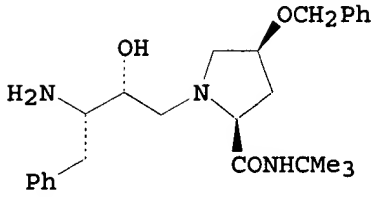
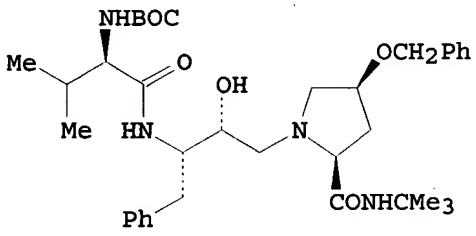



II



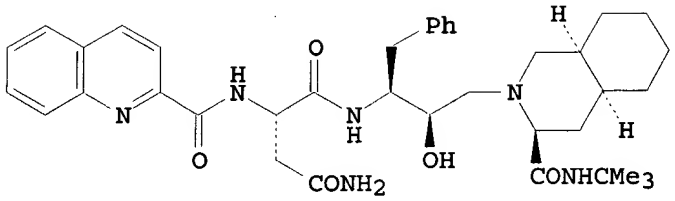

III

AB The title compds., (S)-pyrrolidine-2-carboxamides I (X = acyl, alkoxycarbonyl, etc.; B = bond, aminocarbonyl linkage, etc.; R1 = alkyl, cycloalkyl; Y = acyl, alkylsulfonyl, etc.) and their uses for the treatment of HIV infections in humans (virucides) is claimed. A process for the prepn. of I comprises a ring opening reaction of an epoxide deriv. with an (S)-2-pyrrolidinecarboxamide deriv. For example, coupling of a valine deriv. with protected 1-[3(S)-amino-2(R)-hydroxy-4-phenylbutyl]-4(S)-benzyloxy-2(S)-pyrrolidinecarboxamide (II) gave 4(S)-benzyloxy-1-[3(S)-[[N-(benzyloxycarbonyl)valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-2(S)-pyrrolidinecarboxamide III. The in vitro inhibitory concn. for HIV protease for III was 150 nM.

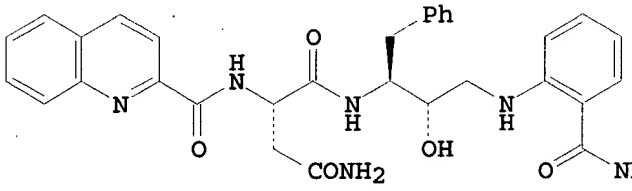
IT **152892-87-0P 152892-89-2P 152892-90-5P**
**152892-95-0P 152892-99-4P 152893-00-0P**
**152893-01-1P 152893-02-2P 152893-05-5P**
**152983-98-7P 152984-00-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as **HIV protease inhibitor** (virucide))

L9 ANSWER 54 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1994:107712 CAPLUS
DN 120:107712
TI The synthesis of novel HIV-protease inhibitors via silica gel assisted addition of amines to epoxides
AU Bennett, Frank; Patel, Naginbhai M.; Girijavallabhan, Viyyoor M.; Ganguly, Ashit K.
CS Schering-Plough Res. Inst., Kenilworth, NJ, 07033, USA
SO Synlett (1993), (9), 703-4

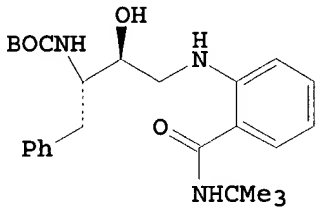
CODEN: SYNLES; ISSN: 0936-5214
DT Journal
LA English
OS CASREACT 120:107712
GI



I



II



III

AB HIV-protease inhibitors, contg. novel .beta.-hydroxy secondary amine transition state isosteres, are constructed using a silica gel mediated addn. of unreactive amines to epoxides as the key step. Virally encoded aspartic protease from HIV-1 is a target for chemotherapeutic intervention of AIDS. Blocking of this enzyme results in termination of post-translational processing of viral gag and gag-pol polyprotein gene products and prodn. of non-infectious virions. An analog of the known .beta.-hydroxy ethylamine transition state dipeptide isostere I which carry simplified arom. hydrophobic ligands, i.e. the compd. II, was prepd. A key step in the synthetic sequence was the silica gel-mediated aminolysis of epoxides with anthranilate derivs. to give intermediates, such as III.

IT **127779-20-8P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(prepn. of, as **HIV protease inhibitor**
)

L9 ANSWER 55 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1994:94796 CAPLUS
DN 120:94796
TI Peptide mimetics as enzyme inhibitors: Use of free energy perturbation calculations to evaluate isosteric replacement for amide bonds in a potent HIV protease inhibitor
AU Cieplak, Piotr; Kollman, Peter A.
CS Dep. Pharm. Chem., Univ. California, San Francisco, CA, 94143, USA
SO J. Comput.-Aided Mol. Des. (1993), 7(3), 291-304
CODEN: JCADEQ; ISSN: 0920-654X
DT Journal
LA English
AB The authors present the application of free energy perturbation theory/mol. dynamics to predict the consequence of replacing each of the seven peptide bonds in the potent HIV protease inhibitor JG365: ACE (acetyl)-Ser-Leu-Asn-HEA (hydroxyethylamine analog of Phe-Pro)-Ile-Val-NME (N-methyl) by ethylene or fluoroethylene isosteres. Replacing two of these bonds may well lead to significantly tighter binding; replacing two others is predicted to significantly diminish the binding affinity. Also, for three of the peptide bonds fluoroethylene replacements could lead to increased binding of free energies of the inhibitors. The authors' results should be considered as predictive since there are, as yet, no exptl. results on such peptide replacements as enzyme inhibitors.
IT **132748-20-0**, JG 365
RL: BIOL (Biological study)
(**protease inhibition** by, in **HIV**,
QSAR of)

L9 ANSWER 56 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1994:94447 CAPLUS
DN 120:94447
TI Design and structure of symmetry-based inhibitors of HIV-1 protease
AU Erickson, John W.
CS Struct. Biochem. Program, PRI/Dyn Corp., Frederick, MD, 21702, USA
SO Perspect. Drug Discovery Des. (1993), 1(1), 109-28
CODEN: PDDDEC
DT Journal; General Review
LA English
AB A review with 50 refs. on the design of novel series of C2-symmetry-based inhibitors of HIV-1 protease.
IT **152886-86-7D**, derivs.
RL: BIOL (Biological study)
(as **HIV-1 protease inhibitors**,
against HIV-1, for treatment of AIDS, in humans, structure in relation to)

L9 ANSWER 57 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1994:68731 CAPLUS
DN 120:68731
TI Inactivation of a yeast transactivator by the fused HIV-1 proteinase: A simple assay for inhibitors of the viral enzyme activity
AU Murray, Michael G.; Hung, Wesley; Sadowski, Ivan; Das Mahapatra, Bimalendu
CS Schering-Plough Res. Inst., Kenilworth, NJ, 07033-0539, USA
SO Gene (1993), 134(1), 123-8
CODEN: GENED6; ISSN: 0378-1119
DT Journal
LA English
AB The human immunodeficiency virus type 1 (HIV-1) proteinase (PR) and its flanking sequences have been fused in frame between the DNA-binding domain and the transcription-activation domain of the yeast protein, GAL4. As has been shown before with the 3C proteinase of Coxsackie virus B3 (CVB3), the GAL4::PR fusion protein retains its GAL4 function, providing the PR is inactive. When PR is active, its autocatalytic activity in the hybrid protein is shown to inactivate the transactivation function of GAL4. This provides a simple assay to monitor PR activity. A dose-dependent effect of a potent PR-specific inhibitor (SCH 52852) is demonstrated in this system and illustrates the sensitivity of the assay. The assay is used for high throughput screening to identify novel inhibitors of the viral PR, and provides a method to generate and analyze mutants and revertants of the PR.
IT **127779-20-8**, Sch 52852
RL: ANST (Analytical study)
(**HIV-1 proteinase inhibition** by, fusion product with yeast GAL4 protein in assay of)

L9 ANSWER 58 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1993:603375 CAPLUS
DN 119:203375
TI Potent HIV protease inhibitors: the development of tetrahydrofuranylglycines as novel P2-ligands and pyrazine amides as P3-ligands
AU Ghosh, Arun K.; Thompson, Wayne J.; Holloway, M. Katharine; McKee, Sean P.; Duong, Tien T.; Lee, Hee Yoon; Munson, Peter M.; Smith, Anthony M.; Wai, Jenny M.; et al.
CS Dep. Med. Chem., Merck Res. Lab., West Point, PA, 19486, USA
SO J. Med. Chem. (1993), 36(16), 2300-10
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CASREACT 119:203375; CJACS
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A series of protease inhibitors bearing constrained unnatural amino acids at the P2-position and novel heterocycles at the P3-position of compd. I (R = R1; Ro 31-8959) were synthesized, and their in vitro enzyme inhibitory and antiviral activities were evaluated. Replacement of P2-asparagine of compd. I (R = R1) with (2S,3'R)-tetrahydrofuranylglycine resulted in improvement in enzyme inhibitory as well as antiviral potencies (compd. I; R = R2). Interestingly, incorporation of (2S,3'S)-tetrahydrofuranylglycine at the P2-position proved to be less effective. The resulting compd. I (R = R3) was 100-fold less potent than the 2S,3R-isomer (compd. I; R = R2). This stereochem. preference indicated a hydrogen-bonding interaction between the tetrahydrofuranyl oxygen and the residues of the S2-region of the enzyme active site. Furthermore, replacement of P3-quinolinoyl ligand of I (R = R1) with various novel heterocycles resulted in potent inhibitors of HIV proteases. Of particular interest, compd. I (R = R4) with (2S,3'R)-tetrahydrofuranylglycine at P2 and pyrazine deriv. at P3 is one of the most potent inhibitors of HIV-1 (IC50 value 0.07 nM) and HIV-2 (IC50 value 0.18 nM) proteases. Another important result in this series is the identification of compd. I (R = R5) in which the P2-P3-amide carbonyl has been removed. The resulting compd. I (R = R5) has exhibited improvement in antiviral potency while retaining the enzyme inhibitory potency similar to compd. I (R = R1).

IT **127779-20-8DP**, analogs **146255-24-5P**
**146278-31-1P 150331-78-5P 150331-82-1P**
**150331-83-2P 150331-84-3P 150331-88-7P**
**150331-89-8P 150331-90-1P 150331-91-2P**
**150331-92-3P 150331-93-4P 150331-94-5P**
**150331-95-6P 150331-96-7P 150406-29-4P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn., **HIV-1 protease inhibition** and antiviral activity of)

IT **150331-87-6P 150406-28-3P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn., S-oxidn., **HIV-1 protease inhibition** and antiviral activity of)

L9 ANSWER 59 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1993:603319 CAPLUS
DN 119:203319
TI Preparation of decahydroisoquinolinecarboxamides as HIV protease

inhibitors

IN Thompson, Wayne J.; Ghosh, Arun K.; Lee, Hee Yoon; Huff, Joel R.

PA Merck and Co., Inc., USA

SO Eur. Pat. Appl., 30 pp.
CODEN: EPXXDW

DT Patent

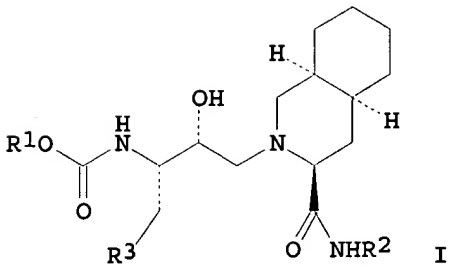
LA English

FAN.CNT 1

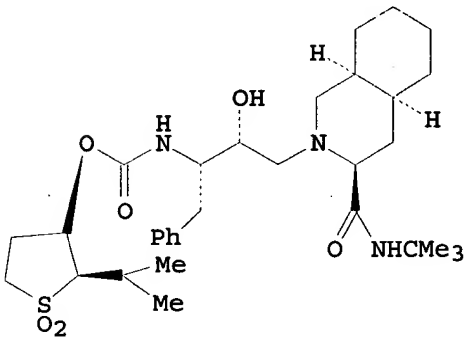
| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | EP 539192 | A1 | 19930428 | EP 92-309639 | 19921021 |
| | EP 539192 | B1 | 19990107 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| | WO 9308184 | A1 | 19930429 | WO 92-US8758 | 19921014 |
| | W: BG, CS, FI, HU, KR, NO, PL, RO, RU | | | | |
| | CA 2081134 | AA | 19930424 | CA 92-2081134 | 19921022 |
| | AU 9227253 | A1 | 19930429 | AU 92-27253 | 19921022 |
| | AU 649170 | B2 | 19940512 | | |
| | ZA 9208164 | A | 19930503 | ZA 92-8164 | 19921022 |
| | JP 05239031 | A2 | 19930917 | JP 92-309474 | 19921023 |
| | JP 06078314 | B4 | 19941005 | | |
| | US 5502060 | A | 19960326 | US 94-328936 | 19941025 |
| PRAI | US 91-781470 | 19911023 | | | |
| | US 92-929991 | 19920821 | | | |
| | US 93-144094 | 19931027 | | | |

OS MARPAT 119:203319

GI



I



II

AB Title compds. [I; R1 = (unsatd.) (substituted) 5-7 membered carbocyclyl, heterocyclyl; R2 = (substituted) alkyl, (substituted) (unsatd.) 5-7 membered carbocyclyl; R3 = (substituted) Ph, cycloalkyl], were prepd. Thus, 2(R,S)-methylethyl-3(R,S)-tetrahydrothienyl 2-pyridyl carbonate (prepn. given) and N-tert-Bu decahydro-2-(2R-hydroxy-4-phenyl-3S-aminobutyl)-(4aS,8aS)-isoquinoline-3S-carboxamide (prepn. given) were stirred with Et3N in CH2Cl2 to give the diamide, which was S-oxidized with N-methylmorpholine oxide/OsO4 in actone/H2O/Me3COH to give, after chromatog., title compd. II. II inhibited HIV protease with IC50 = 4 nM.

IT **145631-02-3P 145631-07-8P 145631-08-9P**
**145680-05-3P 145680-06-4P 146611-25-8P**
**147949-29-9P 147949-30-2P 147977-17-1P**
**147977-21-7P 150330-55-5P 150330-56-6P**
**150330-57-7P 150330-58-8P 150330-59-9P**
**150330-60-2P 150330-61-3P 150330-62-4P**
**150330-63-5P 150330-64-6P 150330-65-7P**
**150330-66-8P 150330-67-9P 150406-19-2P**
**150406-20-5P 150406-21-6P 150406-22-7P**
**150406-23-8P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as **HIV protease inhibitor**

)

L9 ANSWER 60 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1993:485387 CAPLUS
DN 119:85387
TI A symmetric inhibitor binds HIV-1 protease asymmetrically
AU Dreyer, Geoffrey B.; Boehm, Jeffrey C.; Chenera, Balan; DesJarlais, Renee L.; Hassell, Anne M.; Meek, Thomas D.; Tomaszek, Thaddeus A., Jr.; Lewis, Mitchell
CS Dep. Med. Chem., SmithKline Beecham Pharm., King of Prussia, PA, 19406, USA
SO Biochemistry (1993), 32(3), 937-47
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
OS CJACS
AB Potential advantages of C2-sym. inhibitors designed for the sym. HIV-1 protease include high selectivity, potency, stability, and bioavailability. Pseudo-C2-sym. monools and C2-sym. diols, contg. central hydroxymethyl and (R,R)-dihydroxyethyl moieties flanked by a variety of hydrophobic P1/P1' side chains, were studied as HIV-1 protease inhibitors. The monools and diols were synthesized in 8-10 steps from D-(+)-arabitol and D-(+)-mannitol, resp. Monools with Et or iso-Bu P1/P1' side chains were weak inhibitors of recombinant HIV-1 protease (Ki > 10 .mu.M), while benzyl P1/P1' side chains afforded a moderately potent inhibitor (apparent Ki = 230 nM). Diols were 100-10 000.times. more potent than analogous monools, and a wider range of P1/P1' side chains led to potent inhibition. Both classes of compds. exhibited lower apparent Ki values under high-salt conditions. Surprisingly, monool and diol HIV-1 protease inhibitors were potent inhibitors of porcine pepsin, a prototypical asym. monomeric aspartic protease. These results were evaluated in the context of the pseudosym. structure of monomeric aspartic proteases and their evolutionary kinship with the retroviral proteases. The X-ray crystal structure of HIV-1 protease complexed with a sym. diol was detd. at 2.6 .ANG.. Contrary of expectations, the diol binds the protease asym. and exhibits 2-fold disorder in the electron d. map. Mol. dynamics simulations were conducted beginning with asym. and sym. HIV-1 protease/inhibitor mode complexes. A more stable trajectory resulted from the asym. complex, in agreement with the obsd. asym. binding mode. A simple four-point model was used to argue more generally that van der Waals and electrostatic force fields can commonly lead to an asym. assocn. between sym. mols.
IT **129467-48-7P 142285-33-4P 142285-35-6P**
**142285-39-0P 142285-40-3P 142285-41-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and **HIV-1 protease inhibition**
by, structure in relation to)

L9 ANSWER 61 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1993:409161 CAPLUS
DN 119:9161
TI HIV protease inhibitors
IN Mimoto, Tsutomu; Hattori, Naoko; Nagano, Yuuichi; Shintani, Makoto; Kiso, Yoshiaki
PA Nippon Mining Co., Ltd., Japan
SO Eur. Pat. Appl., 86 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | EP 490667 | A2 | 19920617 | EP 91-311549 | 19911211 |
| | EP 490667 | A3 | 19930505 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| | CA 2056911 | AA | 19920612 | CA 91-2056911 | 19911204 |
| | JP 05170722 | A2 | 19930709 | JP 91-348705 | 19911205 |
| | JP 2700511 | B2 | 19980121 | | |
| | AU 9188900 | A1 | 19920618 | AU 91-88900 | 19911206 |
| | AU 653972 | B2 | 19941020 | | |
| | ZA 9109721 | A | 19921230 | ZA 91-9721 | 19911210 |
| | FI 9105819 | A | 19920612 | FI 91-5819 | 19911211 |
| | NO 9200023 | A | 19920727 | NO 92-23 | 19920102 |
| PRAI | JP 90-409673 | 19901211 | | | |
| | JP 91-25755 | 19910125 | | | |
| | JP 91-89976 | 19910328 | | | |
| | JP 91-169174 | 19910614 | | | |
| | JP 91-304043 | 19911023 | | | |

OS MARPAT 119:9161
AB A-B1-B2-B3-NHCHR1CH(OH)CO-B4-B5-B6-XR2R3 [A = H, N-protecting group; B1-B6 = (un)substituted amino acid residue, bond; R1 = (un)substituted alkyl, cycloalkyl, aryl, heterocyclic; R2, R3 = H (un)substituted hydrocarbon; X = N, O; R3 absent if X = O] (188 compds.) were prepd. Thus, PhCH2CH2CO-Asn-X1-Pro-Ile-Val-NH2 [X1 = (2R,3S)-NHCH(CH2Ph)CH(OH)CO, I] was prepd. by solid-phase synthesis. HIV protease treated with 1mM I showed 1.5% residual activity.
IT **138228-18-9P 138228-19-0P 138228-20-3P**
**138228-21-4P 138258-64-7P 139694-65-8P**
**139694-67-0P 139757-45-2P 139758-09-1P**
**139758-10-4P 139758-11-5P 139758-12-6P**
**141171-77-9P 141171-80-4P 143909-13-1P**
**143909-14-2P 143909-15-3P 143909-16-4P**
**143909-18-6P 143909-19-7P 143909-20-0P**
**143909-21-1P 143909-22-2P 143909-23-3P**
**143909-24-4P 143909-25-5P 143909-26-6P**
**143909-28-8P 143909-29-9P 143909-30-2P**

**143909-31-3P 143909-35-7P 143909-36-8P**
**143934-16-1P 143934-17-2P 143934-18-3P**
**143934-19-4P 143934-20-7P 143934-21-8P**
**143934-22-9P 143934-23-0P 143934-24-1P**
**143934-25-2P 143934-26-3P 143934-27-4P**
**143934-28-5P 143934-29-6P 143934-30-9P**
**143934-31-0P 143934-32-1P 143934-34-3P**
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**143934-75-2P 143934-81-0P 143934-89-8P**
**143934-91-2P 143934-92-3P 143934-95-6P**
**143934-97-8P 143934-98-9P 143934-99-0P**
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**143957-42-0P 144016-87-5P 147657-50-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and **HIV protease-inhibiting** activity of)

IT **143935-56-2P 143935-61-9P 143978-14-7P**
**143978-16-9P 143978-18-1P 143978-23-8P**
**143978-33-0P 143978-38-5P 143978-39-6P**
**143978-54-5P 143978-61-4P 143978-67-0P**
**143978-68-1P 143978-70-5P 143978-71-6P**
**143978-72-7P 143978-74-9P 143978-75-0P**
**143978-77-2P 143978-78-3P 143978-80-7P**
**143978-81-8P 143978-83-0P 143978-84-1P**
**143979-32-2P 143979-42-4P 143979-43-5P**
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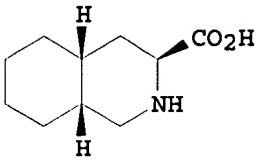
**143979-55-9P 143979-56-0P 144005-44-7P**
**144069-69-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn., deblocking, and **HIV protease-inhibiting** peptide synthesis with)

L9 ANSWER 62 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1993:409149 CAPLUS
DN 119:9149
TI NMR studies of four isomers of decahydroisoquinoline-3(S)-carboxylic acid and a potent HIV proteinase inhibitor incorporating the (S,S,S) isomer
AU Gilbert, Jenny C.; Redshaw, Sally; Simmonite, Heather S.; Thomas, W. Anthony; Whitcombe, Ian W. A.
CS Roche Prod. Ltd., Welwyn Garden City/Herts., AL7 3AY, UK
SO J. Chem. Soc., Perkin Trans. 2 (1993), (3), 475-9

CODEN: JCPKBH; ISSN: 0300-9580
DT Journal
LA English
GI



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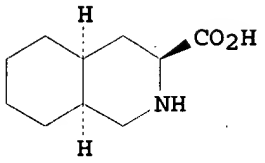

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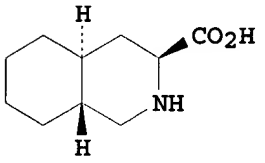

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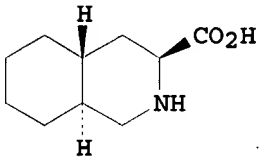

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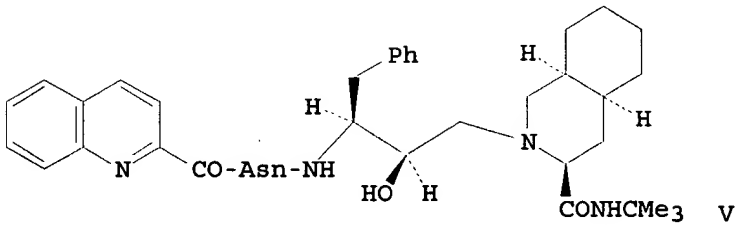


V

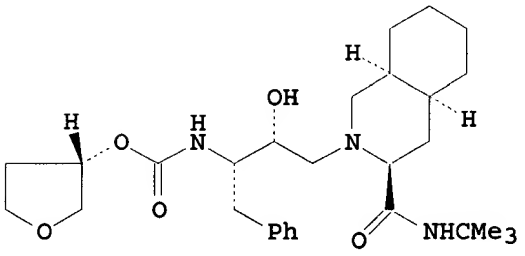
AB The stereochem. and conformations of decahydroisoquinoline-3(S)-carboxylic acid (DHIQ) stereoisomers I-IV have been elucidated by NMR spectroscopy. A potent HIV proteinase inhibitor, Ro 31-8959 (V), incorporating the (S,S,S)-isomer of DHIQ, has also been examd. and crit. conformational features compared with those found in the x-ray structure of the enzyme-bound inhibitor.

IT **128053-46-3 147922-51-8 147922-52-9**
RL: RCT (Reactant)
(**HIV proteinase-inhibiting** activity of)

IT **127779-20-8**
RL: RCT (Reactant)
(conformation and **HIV proteinase-inhibiting** activity of)

L9 ANSWER 63 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1993:408656 CAPLUS
DN 119:8656
TI Cyclic sulfolanes as novel and high-affinity P2 ligands for HIV-1 protease inhibitors
AU Ghosh, Arun K.; Thompson, Wayne J.; Lee, Hee Yoon; McKee, Sean P.;

Munson, Peter M.; Duong, Tien T.; Darke, Paul L.; Zugay, Joan A.; Emini, Emilio A.; et al.
CS Dep. Med. Chem., Mol. Biol., Merck Res. Lab., West Point, PA, 19486, USA
SO J. Med. Chem. (1993), 36(7), 924-7
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CASREACT 119:8656; CJACS
GI

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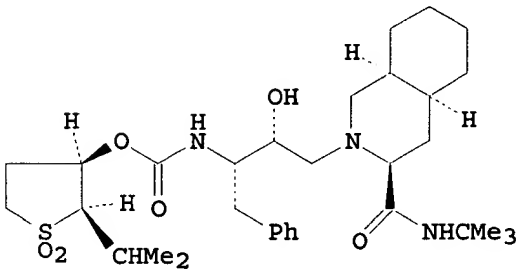



II

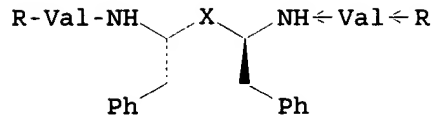
AB Recently the use of urethanes of 3-tetrahydrofuran as P2-ligands for the S2-substrate binding site of HIV-1 protease was reported. The urethane of (S)-3-hydroxy sulfolane substantially increased the in vitro potency of inhibitors relative to the heterocycle 3-tetrahydrofuran. Furthermore, introduction of a small 2-alkyl group cis to the 3-hydroxyl group of either heterocycle system further enhances enzyme affinity. This is consistent with modeling studies using the x-ray crystal structure of the enzyme-inhibitor complex of THF derived inhibitor I and HIV-1 protease. The cis-2-iso-Pr group thus far offers optimum enhancement of the inhibitory properties of the 3-hydroxysulfolane providing an inhibitor II; for HIV-1, IC50 3 nM; for HIV-219, IC50 17 nM) of comparable in vitro antiviral potency to present clin. candidate (3S,4aS,8aS,2'R,3'S)-N-tert-butyl-2-(2'-hydroxy-4'-phenyl-3'-[[[N-(2-

quinolinylcarbonyl)-L-asparaginyl]amino]butyl]-decahydroisoquinoline-3-carboxamide (Ro 31-8959), but of reduced mol. wt. due to the exclusion of the P3-quinoline ligand. A stereoselective and general synthetic route to this novel class of ligands in optically pure form was developed.

IT **145631-07-8 147949-30-2 147949-31-3 147949-32-4 147949-33-5 147949-34-6 147949-35-7 147977-17-1 147977-18-2 147977-19-3 147977-20-6 147977-21-7 147977-22-8**
RL: RCT (Reactant)
(**HIV protease inhibitor**)

IT **147949-29-9P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as **HIV protease inhibitor**
)

L9 ANSWER 64 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1993:234430 CAPLUS
DN 118:234430
TI Symmetry-based inhibitors of HIV protease. Structure-activity studies of acylated 2,4-diamino-1,5-diphenyl-3-hydroxypentane and 2,5-diamino-1,6-diphenylhexane-3,4-diol
AU Kempf, Dale J.; Codacovi, Lynnmarie; Wang, Xiu Chun; Kohlbrenner, William E.; Wideburg, Norman E.; Saldivar, Ayda; Vasavanonda, Sudthida; Marsh, Kennan C.; Bryant, Pamela; et al.
CS Pharm. Prod. Div., Abbott Lab., Abbott Park, IL, 60064, USA
SO J. Med. Chem. (1993), 36(3), 320-30
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CJACS
GI

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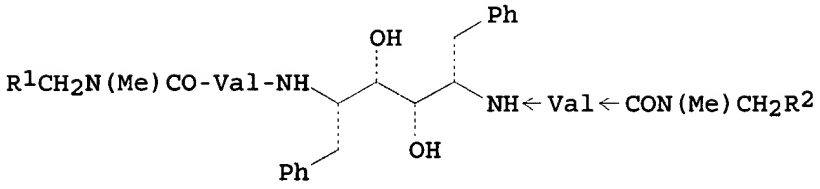
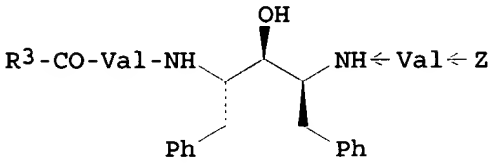
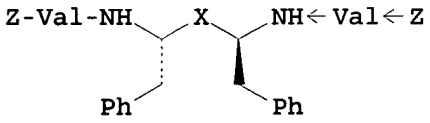



II




III




IV

AB Title sym. substituted compds. I [R = (2-pyridylmethoxy)carbonyl, [2-(4-morpholinyl)ethoxy]carbonyl, trans-3-(2-pyridyl)acryloyl, (2-pyridylmethyl)methylamino]carbonyl, [(2-pyridylmethyl)methylamino]sulfonyl, etc.; X = (R,R)-CH(OH)CH(OH), (R,S)-CH(OH)CH(OH), (S,S)-CH(OH)CH(OH), CH(OH)] were prepd. as inhibitors of human immunodeficiency virus (HIV) protease, the enzyme responsible for maturation of HIV. Unsym. substituted HIV protease inhibitors II (R1 = 2-pyridyl, R2 = 3-pyridyl, 4-thiazolyl, 2-thiazolyl; R1 = 2-pyridyl, 2-thiazolyl, 4-thiazolyl, R2 = 2-aminothizol-4-yl) and unsym. substituted mono-ol inhibitors III [Z = benzyloxycarbonyl; R3 = PhCH2O, 2-pyridylmethoxy, 3-pyridylmethoxy, 4-pyridylmethoxy, (1-methyl-3-piperidinyl)methoxy, (1-methyl-2-piperidinyl)methoxy, 2-(4-morphinyl)ethoxy, 2-(1-pyrrolidinyl)ethoxy, 4-methyl-1-piperazinyl] were also prepd. Structure-activity relationships were studied. Beginning with lead compds. IV, the effect of adding polar, heterocyclic end groups to one or both ends of the sym. or pseudosym. inhibitors was probed. Aq. soly. was enhanced > 1000-fold while maintaining potent inhibition of purified HIV-1 protease and anti-HIV activity in vitro. Pharmacokinetic studies in rats indicated a substantial difference in the absorption properties of mono-ol-based and diol-based inhibitors. The oral bioavailability of inhibitor I [R = (2-pyridylmethoxy)carbonyl, X = CH(OH)] in rats was 19%; however, the Cmax obtained failed to exceed the anti-HIV EC50 in vitro.

Searcher : Shears 308-4994

Substantial plasma levels of potent inhibitors of the diol class were not obtained after oral administration in rats; however, the optimal combination of aq. soly. and in vitro antiviral activity of several inhibitors support their potential use in i.v. therapy.

IT **134805-69-9P 134805-76-8P 134805-77-9P**
**134805-80-4P 134805-82-6P 134805-85-9P**
**134805-89-3P 134878-09-4P 134878-10-7P**
**134878-11-8P 134878-16-3P 134878-17-4P**
**134878-18-5P 134878-19-6P 134878-20-9P**
**134878-21-0P 137828-39-8P 144141-71-9P**
**144141-75-3P 144141-77-5P 144142-36-9P**
**144142-38-1P 144142-39-2P 144142-45-0P**
**144142-46-1P 144142-47-2P 144142-57-4P**
**144142-58-5P 144142-60-9P 144142-61-0P**
**144142-63-2P 144142-64-3P 144154-80-3P**
**144154-81-4P 144162-21-0P 144162-22-1P**
**144162-38-9P 144179-89-5P 144179-94-2P**
**144179-98-6P 144179-99-7P 144180-00-7P**
**144239-35-0P 144239-36-1P 144239-37-2P**
**144239-40-7P 144239-41-8P 144239-42-9P**
**144239-43-0P 147146-07-4P 147146-10-9P**
**147201-57-8P 147201-58-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and **HIV protease-inhibiting** activity of)

L9 ANSWER 65 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1993:204690 CAPLUS
DN 118:204690
TI Kynostatin (KNI)-227 and -272, highly potent anti-HIV agents: conformationally constrained tripeptide inhibitors of HIV protease containing allophenylnorstatine
AU Mimoto, Tsutomu; Imai, Junya; Kisanuki, Sumitsugu; Enomoto, Hiroshi; Hattori, Naoko; Akaji, Kenichi; Kiso, Yoshiaki
CS Dep. Med. Chem., Kyoto Pharm. Univ., Kyoto, 607, Japan
SO Chem. Pharm. Bull. (1992), 40(8), 2251-3
CODEN: CPBTAL; ISSN: 0009-2363
DT Journal
LA English
AB Selective and potent HIV protease inhibitors contg. allophenylnorstatine [Apns; (2S,3S)-3-amino-2-hydroxy-4-phenylbutyric acid] as a transition-state mimic were designed and synthesized. Among them, conformationally constrained tripeptide derivs., kynostatin (KNI)-227 and -272 exhibited highly potent antiviral activities against a wide spectrum of HIV isolates. Ready availability due to the simple synthetic procedure and the excellent antiviral properties indicate that KNI-227 and KNI-272 are promising candidates as selective anti-AIDS drugs.
IT **139694-65-8 141171-77-9**, KNI 144

**141171-80-4 143934-32-1 143934-35-4**
**143934-36-5 143934-41-2 143934-43-4**
**147384-71-2**
RL: BIOL (Biological study)
(**HIV protease inhibiting** activity
of, structure in relation to)

L9 ANSWER 66 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1993:192283 CAPLUS
DN 118:192283
TI amino acid derivatives as HIV-1 protease inhibitors and methods for their synthesis
IN Kempf, Dale J.; Codacovi, Lynn M.; Norbeck, Daniel W.; Plattner, Jacob J.; Sham, Hing L.; Wittenberger, Steven J.; Zhao, Chen
PA Abbott Laboratories, USA
SO Eur. Pat. Appl., 154 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 6

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | EP 486948 | A2 | 19920527 | EP 91-119464 | 19911104 |
| | EP 486948 | A3 | 19930825 | | |
| | R: AT, BE, DE, DK, FR, GB, GR, LU, NL, SE | | | | |
| | AU 9187715 | A1 | 19920521 | AU 91-87715 | 19911108 |
| | AU 650491 | B2 | 19940623 | | |
| | CA 2055670 | AA | 19920521 | CA 91-2055670 | 19911115 |
| | CH 684696 | A | 19941130 | CH 91-3384 | 19911119 |
| | CH 688551 | A | 19971114 | CH 94-3618 | 19911119 |
| | CH 689001 | A | 19980715 | CH 97-2338 | 19911119 |
| | JP 04308574 | A2 | 19921030 | JP 91-354231 | 19911120 |
| | ES 2070660 | A1 | 19950601 | ES 91-2579 | 19911120 |
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| | US 5354866 | A | 19941011 | US 93-121673 | 19930914 |
| | US 5541334 | A | 19960730 | US 95-409380 | 19950323 |
| | US 5597926 | A | 19970128 | US 95-409767 | 19950323 |
| | US 5616714 | A | 19970401 | US 95-410260 | 19950324 |
| | US 5648497 | A | 19970715 | US 95-410623 | 19950324 |
| | US 5837873 | A | 19981117 | US 95-410162 | 19950324 |
| | US 5539122 | A | 19960723 | US 95-410996 | 19950327 |
| | US 5552558 | A | 19960903 | US 95-411032 | 19950327 |
| | US 5696270 | A | 19971209 | US 95-411140 | 19950327 |
| | US 5580984 | A | 19961203 | US 95-412253 | 19950328 |
| | US 5679797 | A | 19971021 | US 95-412244 | 19950328 |
| | US 5583232 | A | 19961210 | US 95-412821 | 19950329 |
| | US 5597927 | A | 19970128 | US 95-412438 | 19950329 |
| | US 5674882 | A | 19971007 | US 95-413136 | 19950329 |
| | US 5583233 | A | 19961210 | US 95-413290 | 19950330 |

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| | US 5625072 | A | 19970429 | US 95-415827 | 19950403 |
| | US 5591860 | A | 19970107 | US 95-416272 | 19950404 |
| | US 5597928 | A | 19970128 | US 95-416607 | 19950404 |
| | US 5608072 | A | 19970304 | US 95-416259 | 19950404 |
| | US 5565418 | A | 19961015 | US 95-417304 | 19950405 |
| | US 5659044 | A | 19970819 | US 95-417165 | 19950405 |
| | US 5659045 | A | 19970819 | US 95-417295 | 19950405 |
| | US 5616720 | A | 19970401 | US 95-418056 | 19950406 |
| | US 5635523 | A | 19970603 | US 95-417879 | 19950406 |
| | US 5554783 | A | 19960910 | US 95-418978 | 19950407 |
| | US 5541206 | A | 19960730 | US 95-423387 | 19950425 |

PRAI US 90-616170 19901120
US 91-746020 19910815
US 91-777626 19911023
US 94-270210 19940823
US 83-355945 19830523
US 89-355945 19890523
US 89-405604 19890908
US 89-456124 19891222
US 90-518730 19900509
US 92-998114 19921229
US 93-121673 19930914
US 93-158587 19931202

OS CASREACT 118:192283; MARPAT 118:192283

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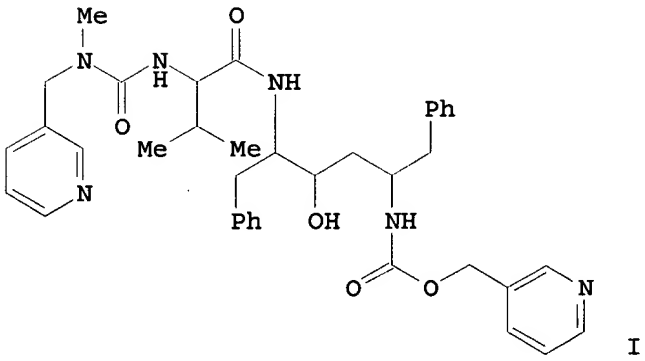



I

AB Certain 2-alkoxy-1,4-butanediamine derivs. are claimed. Specific compds. such as (2S,3S,5S)-2-[N-[N-[N-methyl-N-[(2-pyridyl)methyl]amino]carbonyl]valinyl]amino]-5-[N-[[(3-pyridinyl)methoxycarbonyl]amino]-1,6-diphenyl-3-hydroxyhexane I, their salts, and prodrug forms thereof are claimed. The use of such compds. for the manuf. of pharmaceuticals for the treatment of HIV

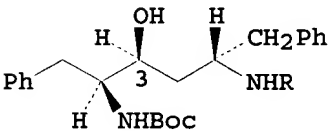
infections and their use for the inhibition of HIV protease are claimed. I in vivo was an HIV-1 protease inhibitor and it was active against HIV-13b.

IT **137649-69-5 144163-85-9 144163-90-6 144186-45-8 144239-97-4**
RL: RCT (Reactant)
(intermediate for **HIV protease inhibitor**)

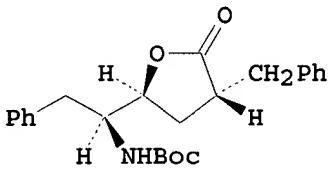
IT **144141-68-4P 144141-69-5P 144141-70-8P 144141-71-9P 144141-75-3P 144141-76-4P 144141-77-5P 144141-78-6P 144141-79-7P 144141-82-2P 144141-83-3P 144141-84-4P 144141-85-5P 144141-86-6P 144141-90-2P 144141-91-3P 144141-92-4P 144141-95-7P 144141-96-8P 144141-97-9P 144141-98-0P 144141-99-1P 144142-00-7P 144142-01-8P 144142-02-9P 144142-03-0P 144142-04-1P 144142-05-2P 144142-06-3P 144142-07-4P 144142-08-5P 144142-09-6P 144142-10-9P 144142-11-0P 144142-12-1P 144142-13-2P 144142-14-3P 144142-15-4P 144142-16-5P 144142-17-6P 144142-18-7P 144142-19-8P 144142-20-1P 144142-21-2P 144142-22-3P 144142-23-4P 144142-24-5P 144142-25-6P 144142-26-7P 144142-27-8P 144142-28-9P 144142-29-0P 144142-30-3P 144142-31-4P 144142-32-5P 144142-33-6P 144142-34-7P 144142-35-8P 144142-36-9P 144142-37-0P 144142-38-1P 144142-39-2P 144142-40-5P 144142-41-6P 144142-42-7P 144142-43-8P 144142-44-9P 144142-45-0P 144142-46-1P 144142-47-2P 144142-48-3P 144142-51-8P 144142-52-9P 144142-53-0P 144142-54-1P 144142-55-2P 144142-56-3P 144142-57-4P 144142-58-5P 144142-59-6P 144142-60-9P 144142-61-0P 144142-62-1P 144142-63-2P 144142-64-3P 144142-65-4P 144142-66-5P 144142-68-7P 144142-69-8P 144142-92-7P 144142-93-8P 144142-94-9P 144142-95-0P 144142-96-1P 144142-97-2P 144143-00-0P 144143-02-2P 144143-03-3P 144143-04-4P 144143-05-5P 144143-06-6P 144143-07-7P 144143-08-8P 144143-09-9P 144154-80-3P 144154-81-4P 144162-17-4P 144162-18-5P 144162-19-6P 144162-20-9P 144162-21-0P 144162-22-1P 144162-23-2P 144163-01-9P 144163-04-2P 144163-05-3P 144164-27-2P 144179-89-5P 144179-90-8P 144179-91-9P 144179-92-0P 144179-93-1P 144179-94-2P**

**144179-95-3P 144179-96-4P 144179-97-5P**
**144179-98-6P 144179-99-7P 144180-00-7P**
**144180-01-8P 144180-02-9P 144202-12-0P**
**144239-34-9P 144239-35-0P 144239-36-1P**
**144239-37-2P 144239-38-3P 144239-39-4P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as **HIV-1 protease inhibitor**)

L9 ANSWER 67 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1993:169576 CAPLUS
DN 118:169576
TI Potent HIV-1 protease inhibitors: stereoselective synthesis of a dipeptide mimic
AU Ghosh, Arun K.; McKee, Sean P.; Thompson, Wayne J.; Darke, Paul L.; Zugay, Joan C.
CS Dep. Med. Chem. Mol. Biol., Merck Res. Lab., West Point, PA, 19486, USA
SO J. Org. Chem. (1993), 58(5), 1025-9
CODEN: JOCEAH; ISSN: 0022-3263
DT Journal
LA English
OS CASREACT 118:169576; CJACS
GI




I



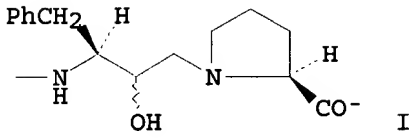

II

AB The synthesis of a differentially protected dipeptide mimic I (R = CO2CH2Ph, Boc = CO2CMe3) in enantiomerically pure form is described. The key step involves the epimerization of the C-2 center of the lactone II, hydrolysis and protection of the resulting hydroxy acid, followed by Curtius rearrangement to introduce the urethane functionality. The scope and versatility of this isostere has been demonstrated by its conversion to potent HIV-1 protease inhibitors with nanomolar potencies. Also, the 3S hydroxyl configuration of the dipeptide isostere I is the preferred configuration for its potency, as established through the synthesis of I (R = Boc) and its 3R diastereomer. The present synthesis is efficient and provides an access to other dipeptide mimics with a great deal of structural diversity.
IT **144141-82-2P 144239-47-4P 146500-10-9P**

**146500-11-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and **HIV-1 protease inhibitory** activity of)

L9 ANSWER 68 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1992:644974 CAPLUS
DN 117:244974
TI Peptide inhibitors of HIV-1 protease containing phenylnorstatine as a transition state element
AU Raju, Bore G.
CS Univ. Hosp., Boston, MA, 02118, USA
SO Pept.: Chem. Biol., Proc. Am. Pept. Symp., 12th (1992), Meeting Date 1991, 729-31. Editor(s): Smith, John A.; Rivier, Jean E. Publisher: ESCOM, Leiden, Neth.
CODEN: 57XGA9
DT Conference
LA English
AB To date there are no reports of inhibitors of HIV-1 protease contg. phenylnorstatine as the nonhydrolyzable isostere. The present work describes the stereochem. requirements for phenylnorstatine to serve as a transition state element when incorporated in substrate analogs, and explores different substrate sequences as a starting point to develop inhibitors of HIV-1 protease. Synthesis of 4 possible isomers of 3-amino-2-hydroxy-4-phenylbutanoic acid (phenylnorstatine, AHPBA) was achieved by a modification of the reported procedure. The optically pure amino acids were incorporated in peptide sequences by soln. phase techniques. HPLC based on HIV-1 protease assay was performed as described.
IT **137682-13-4 137766-52-0 137766-54-2**
RL: BIOL (Biological study)
(as **HIV-1 protease inhibitor**, structure in relation to)

L9 ANSWER 69 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1992:592318 CAPLUS
DN 117:192318
TI New hydroxyethylamine HIV protease inhibitors that suppress viral replication
AU Rich, Daniel H.; Prasad, J. V. N. Vara; Sun, Chong Qing; Green, Jeremy; Mueller, Richard; Houseman, Kathryn; MacKenzie, Debra; Malkovsky, Miroslav
CS Sch. Pharm., Univ. Wisconsin, Madison, WI, 53706, USA
SO J. Med. Chem. (1992), 35(21), 3803-12
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CJACS
GI




I

AB The synthesis of analogs of Ac-Ser-Leu-Asn-[Phe-HEA-Pro]-Ile-Val-OMe (JG-365; Phe-HEA-Pro = hydroxyethylamine transition state analog I), a tight-binding inhibitor of human immunodeficiency virus protease (HIVP), are reported. Systematic modification of the P3 and P3' regions of the inhibitors has led to smaller HIVP inhibitors that inhibit viral replication in HIV-infected and simian immunodeficiency virus (SIV)-infected cell cultures. Six aliph. and arom. derivs. were prepd. by replacing residues in the P3 regions of Boc-Leu-Asn-[Phe-HEA-Pro]-Ile-Val-OMe (Boc = Me3CO2C). Arom. side chains at P3 gave better inhibitors than aliph. side chains. The better inhibitors in this series contained a .beta.-naphthylalanine or a biphenyl unit at P3. A second series of HIVP inhibitors were obtained by converting the P3 group into acyl groups. R-Asn-[Phe-HEA-Pro]-Ile-Phe-OMe (R = PhCH2O2C, 2-quinolinylcarbonyl) are potent HIVP inhibitors with Ki values equal to 1.0 and 0.1 nM, resp. The inhibition consts. were det. by using the continuous fluorometric assay developed by M. V. Toth and G. R. Marshall (1990). The activities of the protease inhibitors for inhibition of SIV replication were detd. in vitro using CEMx174 cells. Inhibition of HIV infection was detd. essentially as reported by R. Pauwels, et. al. (1988). The anti-HIV assay was carried out in culture using CEM cells (a CD4+ lymphocyte line) infected with virus strain HTLV-IIIb with a multiplicity of infection of 0.1. Several analogs inhibited the cytopathic effect at concns. of 0.1-0.8 .mu.g/mL. These results establish that good inhibitors of HIV protease that inhibit viral replication in infected lymphocytes in in vitro cell assays can be obtained from JG-365 when the Ac-Ser-Leu unit is replaced by arom. acyl derivs.

IT **127231-46-3P 127306-17-6P 132234-39-0P**
**132339-14-1P 137515-64-1P 137622-86-7P**
**143347-94-8P 143347-95-9P 143347-96-0P**
**143347-97-1P 143347-98-2P 143347-99-3P**
**143348-00-9P 143348-01-0P 143348-02-1P**
**143348-03-2P 143348-04-3P 143348-05-4P**
**143348-06-5P 143348-07-6P 143348-08-7P**
**143348-09-8P 143395-67-9P 143395-68-0P**
**143395-69-1P 143395-70-4P 143395-71-5P**
**143395-72-6P 143395-73-7P 143395-74-8P**
**143395-75-9P 143395-76-0P 143395-77-1P**
**143395-78-2P 143395-79-3P 143395-80-6P**

**143395-81-7P 143395-82-8P 143395-83-9P**
**143395-84-0P 143395-85-1P 143395-86-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and **HIV protease inhibitory** activity of)

L9 ANSWER 70 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1992:512027 CAPLUS
DN 117:112027
TI A series of potent HIV-1 protease inhibitors containing a hydroxyethyl secondary amine transition state isostere: synthesis, enzyme inhibition, and antiviral activity
AU Tucker, Thomas J.; Lumma, William C., Jr.; Payne, Linda S.; Wai, Jenny M.; De Solms, S. Jane; Giuliani, Elizabeth A.; Darke, Paul L.; Heimbach, Jill C.; Zugay, Joan A.; et al.
CS Merck Res. Lab., West Point, PA, 19486, USA
SO J. Med. Chem. (1992), 35(14), 2525-33
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CASREACT 117:112027; CJACS
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A series of HIV-1 protease inhibitors contg. a novel hydroxyethyl secondary amine transition state isostere, e.g. I [R = Me3CO2C (Boc)] (II), were prepd. Thus, the alumina-catalyzed ring opening of epoxide III with amide IV gave II. The compds. exhibit a strong preference for the (R) stereochem. at the transition state hydroxyl group. Mol. modeling studies with the prototype compd. II have provided important important insights into the structural requirements for good inhibitor-active site binding interaction. N-terminal extension from II into the P2'-P3 region led to the discovery of I [R = Qua-Asn (Qua = 2-quinolylcarbonyl)] (V), the most potent enzyme inhibitor in the series (IC50 = 5.4 nM). V was shown to have potent antiviral activity in cultured MT-4 human T-lymphoid cells. Comparison of analogs of V with analogs of HIV protease inhibitor Ro31-8959 demonstrate that considerably different structure-activity relationships exist between these two subclasses of hydroxyethylamine HIV-protease inhibitors.
IT **142580-65-2P 142580-66-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and **human immunodeficiency virus-1 protease-inhibiting** activity of)

L9 ANSWER 71 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1992:420008 CAPLUS
DN 117:20008
TI HIV proteinase inhibitors
AU Roberts, Noel A.; Craig, J. Charles; Duncan, Ian B.
CS Dep. Chemother., Roche Prod. Ltd., Welwyn Garden City/Herts, AL7 3AY, UK
SO Biochem. Soc. Trans. (1992), 20(2), 513-16
CODEN: BCSTB5; ISSN: 0300-5127
DT Journal
LA English
AB The development and mode of action of the HIV proteinase inhibitor Ro 318959 is discussed. Antiviral efficacy and an additive inhibition of HIV-1 with dideoxycytidine and AZT are shown.
IT **127779-20-8**
RL: BIOL (Biological study)
(**human immunodeficiency virus**
inhibition by, aspartic **proteinase inhibition**
in)

L9 ANSWER 72 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1992:227702 CAPLUS
DN 116:227702
TI Intriguing structure-activity relations underlie the potent inhibition of HIV protease by norstatine-based peptides
AU Tam, Tim F.; Carriere, Julie; MacDonald, I. David; Castelhano, Arlindo L.; Pliura, Diana H.; Dewdney, Nolan J.; Thomas, Everton M.; Bach, Chinh; Barnett, Jimmy; et al.
CS Syntex Res. Canada, Mississauga, ON, L5N 3X4, Can.
SO J. Med. Chem. (1992), 35(7), 1318-20
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CJACS
AB Phenylnorstatine contg. peptides extending from the P2 to P1' positions, with L-proline at the P1' position and S-stereochem. of the P1 component, exhibit impressive potency vs. HIV-1 potease (IC50 = 0.58-7.4 nM). Representative ketoamides are also active with slightly lower potency. Analogous hydroxyethylamines have previously been reported to be potent inhibitors of this enzyme. The presence of an addnl. carbonyl in this series of proline-based inhibitors enhances their potency, and alters structure-activity relations profoundly. Whereas divergent effects on potency have been obsd. for epimeric hydroxyethylamines upon extension of such P1' terminal peptides to P3' with Ile-Val, lengthening of norstatine contg.-inhibitors in the same fashion, dramatically increases the potency of the R-diastereomer and leaves the IC50 of the S-epimer essentially unchanged. Most interestingly, amino acid residues in

the P1' position contg. parent and fused piperidines lower activity in the norstatine series. By contrast, significant enhancements in inhibitor potency were reported in the hydroxyethylamine series for such proline replacements. Conformational preferences of 6 member rings influenced by A1,3-strain may contribute to the redn. in potency obsd. for the norstatine contg. peptides.

IT **132234-32-3 132339-14-1 137515-64-1**
**137622-86-7 139694-65-8 139758-12-6**
**141171-72-4 141171-73-5 141171-74-6**
**141171-76-8 141171-77-9 141171-78-0**
**141171-79-1 141171-80-4 141171-81-5**
**141171-82-6 141197-75-3 141269-68-3**
RL: BIOL (Biological study)
(**human immunodeficiency virus** 1
**protease inhibition** by)

L9 ANSWER 73 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1992:143332 CAPLUS
DN 116:143332
TI KNI-102, a novel tripeptide HIV protease inhibitor containing allophenylnorstatine as a transition-state mimic
AU Mimoto, Tsutomu; Imai, Junya; Tanaka, Shigeki; Hattori, Naoko; Kisanuki, Sumitsugu; Akaji, Kenichi; Kiso, Yoshiaki
CS Dep. Med. Chem., Kyoto Pharm. Univ., Kyoto, 607, Japan
SO Chem. Pharm. Bull. (1991), 39(11), 3088-90
CODEN: CPBTAL; ISSN: 0009-2363
DT Journal
LA English
AB HIV-1 protease inhibitors contg. allophenylnorstatine[Apns; (2S,3S)-3-amino-2-hydroxy-4-phenylbutyric acid]-Pro (syn diastereomer) as a transition-state mimic were established to be potent and highly selective. Z-Asn-Apns-Pro-NHBut (KNI-102) is the only tripeptide exhibiting substantial anti-HIV activity and may be of min. size for potent, selective inhibition of HIV protease. Ready availability due to its simple chem. structure and stability should make it valuable for studies of the development of metabolically stable anti-AIDS drugs.

IT **138228-18-9**, KNI 122 **138228-19-0**
**138228-20-3 138228-21-4 138258-64-7**, KNI 93 **139694-65-8**, KNI 102 **139694-67-0**
**139757-45-2 139758-09-1**, KNI 81
**139758-10-4 139758-11-5 139758-12-6**
RL: BIOL (Biological study)
(as **HIV protease inhibitor**,
structure in, antiviral activity in relation to)

L9 ANSWER 74 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1992:120368 CAPLUS
DN 116:120368

TI Novel binding mode of highly potent HIV-proteinase inhibitors incorporating the (R)-hydroxyethylamine isostere
AU Krohn, Antonin; Redshaw, Sally; Ritchie, Jenny C.; Graves, Bradford J.; Hatada, Marcos H.
CS Roche Prod. Ltd., Welwyn Garden City/Hertfordshire, AL7 3AY, UK
SO J. Med. Chem. (1991), 34(11), 3340-2
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CJACS
AB A series of new HIV-1 proteinase (HIV-PR) inhibitors incorporating hydroxyethylamine transition state mimetic has been designed and synthesized. The stereochem. requirement at the hydroxyl group has been found to depend critically both upon the length of the inhibitor and upon the nature of individual residues. Small, highly potent inhibitors contg. the (S,S,S)-decahydroisoquinoline-3-carboxy group in the P1' position show a marked preference for the R configuration at the alc. The x-ray structure of the HIV-PR-Ro31-8959 complex revealed a novel binding mode of the inhibitor to the enzyme.
IT **127231-42-9 127231-45-2 132748-20-0**
RL: BIOL (Biological study)
(**HIV-protease inhibitor**,
hydroxyethylamine isostere in, binding mode of)
IT **137515-64-1P 137515-65-2P 137622-86-7P**
**137622-87-8P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as **HIV protease inhibitor**
, hydroxyethylamine isostere in, binding mode of)
IT **127779-20-8P 136522-18-4P 137622-85-6P**
**137693-11-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as **HIV-protease inhibitor**
, hydroxyethylamine isostere in, binding mode in)

L9 ANSWER 75 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1991:670042 CAPLUS
DN 115:270042
TI Inhibitor stabilization of human immunodeficiency virus type-2 proteinase dimer formation
AU Holzman, Thomas F.; Kohlbrenner, William E.; Weigl, Debra; Rittenhouse, Judith; Kempf, Dale; Erickson, John
CS Pharm. Prod. Div., Abbott Lab., Abbott Park, IL, 60064, USA
SO J. Biol. Chem. (1991), 266(29), 19217-20
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English

AB The authors report the first direct observation of the subunit self-assocn. behavior of highly purified recombinant human immunodeficiency virus type-2 (HIV-2) proteinase. Multiple samples of enzyme were subjected to sedimentation equil. anal. ultracentrifugation sequentially at 8.8.degree. and two pH values in the presence and absence of the C2 sym., peptidomimetic inhibitor A76889. At both pH values the enzyme exhibited sedimentation equil. behavior which fit a monomer-dimer-tetramer model. In the absence of inhibitor, the apparent Kd for dimer formation was less than .apprx.100 .mu.M and the apparent Kd for the weaker dimer-tetramer assocn. was greater than .apprx.100 .mu.M. In the presence of inhibitor, at either pH, dimer formation was more strongly favored as indicated by a .apprx.5-14-fold decrease in the apparent Kd for dimer formation and a .apprx.1.2-4-fold increase in the apparent Kd for tetramer formation. The enhanced formation of dimer and decrease in higher order self-assocd. forms in the presence of an inhibitor is consistent with inhibitor stabilization of an active dimer. The inhibitor-induced stabilization of the dimeric species is consistent with a model for substrate-induced formation of active proteinase dimers in virion assembly.

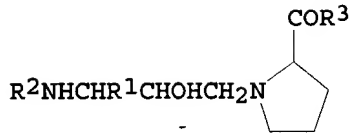
IT **137545-03-0**, A 76889
RL: BIOL (Biological study)
(**human immunodeficiency virus** type 2 **proteinase inhibitor**, proteinase dimer formation stabilization by)

L9 ANSWER 76 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1991:656656 CAPLUS
DN 115:256656
TI Preparation of proline- and asparagine-containing peptides as HIV protease inhibitors
IN Marshall, Garland R.; Rich, Daniel H.; Green, Jeremy; Sun, Chongqing
PA Wisconsin Alumni Research Foundation, USA
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 9108221 | A1 | 19910613 | WO 90-US7059 | 19901203 |

W: JP, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE

PRAI US 89-445070 19891204
OS MARPAT 115:256656
GI



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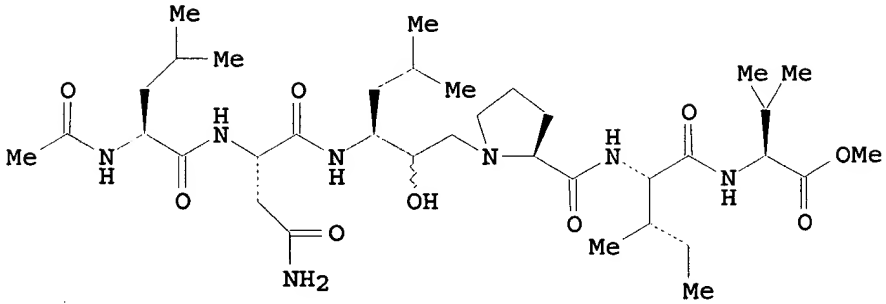


II

AB Proline- and asparagine-contg. peptides I (R1 = Me2CHCH2, CH2Ph, cyclohexylmethyl, alkyl or aralkyl group contg. <12 C atoms; R2, R3 = peptidyl residue where R2 and R3 each contain at least one amino acid residue and at least one of R2 or R3 has at least 2 amino acid residues; R2 contains Asn residue and R2 may contain R4CO, where R4 = aryl) which are protected at both ends by, e.g., 2-aminobenzoic acid at one end, were prepd. as HIV protease inhibitors. Thus, 3S-amino-1-chloro-5-methyl-2-hexanone hydrochloride (prepn. from Boc-Leu-OH.cntdot.H2O given) was coupled with Boc-Asn-OH and the resulting dipeptide was coupled with Boc-Leu-OH and deprotected to give Ac-Leu-Asn-Leu-CH2Cl. This was condensed with Pro-Ile-Val-OMe.cntdot.TosOH (prepn. given) in DMF contg. NaI and NaHCO3 and the resulting aminoketone was reduced by NaBH4 to give title compd. II. I have IC50's < 1 nM against HIV protease.

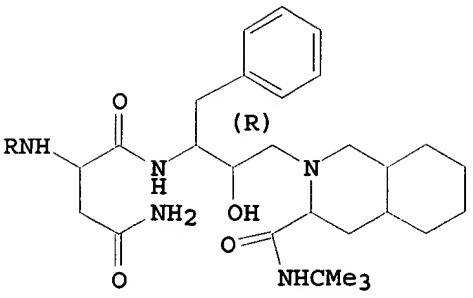
IT **137150-30-2P 137150-31-3P 137150-32-4P**
**137150-33-5P 137150-34-6P 137253-05-5P**
**137253-06-6P 137328-41-7P 137328-43-9P**
**137328-44-0P 137328-45-1P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as **HIV protease inhibitor**
)

L9 ANSWER 77 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1991:656637 CAPLUS
DN 115:256637
TI Preparation of N-(asparaginylaminohydroxyphenylbutyl)decahydroisoquindine-3-carboxamides as HIV protease inhibitors
IN Martin, Joseph Armstrong; Redshaw, Sally
PA Hoffmann-La Roche, F., A.-G., Switz.

SO Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | EP 432695 | A2 | 19910619 | EP 90-123697 | 19901210 |
| | EP 432695 | A3 | 19911218 | | |
| | EP 432695 | B1 | 19950517 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GR, IT, LI, LU, NL, SE | | | | |
| | IN 172553 | A | 19930925 | IN 90-MA905 | 19901112 |
| | US 5196438 | A | 19930323 | US 90-615534 | 19901119 |
| | CA 2030433 | AA | 19910612 | CA 90-2030433 | 19901121 |
| | CA 2030433 | C | 19971021 | | |
| | CZ 280558 | B6 | 19960214 | CZ 90-5765 | 19901121 |
| | FI 9005983 | A | 19910612 | FI 90-5983 | 19901204 |
| | ZA 9009743 | A | 19910828 | ZA 90-9743 | 19901204 |
| | RO 107942 | B1 | 19940131 | RO 90-146474 | 19901204 |
| | HU 56073 | A2 | 19910729 | HU 90-8076 | 19901205 |
| | HU 207298 | B | 19930329 | | |
| | IL 96550 | A1 | 19950315 | IL 90-96550 | 19901205 |
| | AU 9067876 | A1 | 19910613 | AU 90-67876 | 19901207 |
| | AU 634319 | B2 | 19930218 | | |
| | NO 9005322 | A | 19910612 | NO 90-5322 | 19901210 |
| | NO 176566 | B | 19950116 | | |
| | NO 176566 | C | 19950426 | | |
| | GB 2239016 | A1 | 19910619 | GB 90-26776 | 19901210 |
| | GB 2239016 | B2 | 19930804 | | |
| | CN 1052482 | A | 19910626 | CN 90-109931 | 19901210 |
| | CN 1034805 | B | 19970507 | | |
| | BR 9006264 | A | 19910924 | BR 90-6264 | 19901210 |
| | JP 03255076 | A2 | 19911113 | JP 90-409792 | 19901210 |
| | ES 2072959 | T3 | 19950801 | ES 90-123697 | 19901210 |
| | CN 1138983 | A | 19970101 | CN 96-107466 | 19901210 |
| | PL 165225 | B1 | 19941130 | PL 90-288201 | 19901211 |
| | RU 2071470 | C1 | 19970110 | RU 90-4831985 | 19901211 |
| | LT 3682 | B | 19960125 | LT 93-862 | 19930816 |
| | FI 9703895 | A | 19971006 | FI 97-3895 | 19971006 |
| PRAI | GB 89-27913 | 19891211 | | | |
| | FI 90-5983 | 19901204 | | | |

GI




I

AB Title compds. (I; R = PhCH2O2C, 2-quinolinecarbonyl; all undesignated chiral centers are S) were prepd. Thus, N-tert-butyldecahydro-(4aS,9aS)-isoquinoline-(3S)-carboxamide (prepn. given) was condensed with (3S)-benzyloxyformamido-1,2(S)-epoxy-4-phenylbutane in EtOH at 20.degree. over 16 h; the product was hydrogenated and the free amine was coupled with Z-Asn-OH in THF using hydroxybenzotriazole, N-ethylmorpholine, and DCC with ice/salt cooling to give I (R = PhCH2O2C). The latter inhibited HTLV-III infection of C8166 cells with I50 = 20 nM.

IT **127779-20-8P 136522-18-4P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as **HIV protease inhibitor**
)

L9 ANSWER 78 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1990:612686 CAPLUS
DN 113:212686
TI Peptide analogs as human immunodeficiency virus (HIV) protease inhibitors
IN Hanko, Rudolf H.; Scangos, George A.; Yoo-Warren, Heeja; Ramabhadran, Triprayar V.; Paessens, Arnold; Henning, Rolf; Tamburini, Paul Perry; Hoppe, Dieter; Hansen, Jutta; Rabe, Klaus
PA Molecular Therapeutics, Inc., USA
SO Eur. Pat. Appl., 73 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | EP 361341 | A2 | 19900404 | EP 89-117616 | 19890923 |
| | EP 361341 | A3 | 19910703 | | |
| | R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| | FI 8904541 | A | 19900329 | FI 89-4541 | 19890926 |
| | AU 8942308 | A1 | 19900816 | AU 89-42308 | 19890926 |

| | | | | | |
|---|---|---|---|---|---|
| | AU 633017 | B2 | 19930121 | | |
| | DK 8904760 | A | 19900329 | DK 89-4760 | 19890927 |
| | NO 8903834 | A | 19900329 | NO 89-3834 | 19890927 |
| | ZA 8907338 | A | 19900725 | ZA 89-7338 | 19890927 |
| | JP 02191243 | A2 | 19900727 | JP 89-253683 | 19890928 |
| PRAI | US 88-250472 | 19880928 | | | |
| | US 89-386194 | 19890801 | | | |

OS MARPAT 113:212686

GI For diagram(s), see printed CA Issue.

AB A1kZnYmA2 [A1 = H, R1CO; R1 = OR2, NR2R3, CR2R3R4; R2, R3, R4 = (substituted) aliphatyl, aryl; k, n = 0, 1, k = 0 when Z = H; n = 0 when Y = H; Z = H, Ser, Thr, R1CO; Y = H, R5CO; R5 = R1, HNCHR9CO; R9 = (substituted) aliphatyl; A2 = E4E2QE1X, etc; E4 = H, Asn, R1CO; E2 = HNCH(CH2R6)CH(OH)CH2, HNCH(CH2R6)P(OH)(O), etc.; Q = 4-7-membered (hetero)cyclylene; E1 = CO; X = H, R1, HNCHR7R10; R6, R7 = (substituted) aliphatyl, aryl; R10 = H, COR1, CONHCHR9COR1], were prepd. Thus, title compd. I, prepd. by soln. phase methods, had an IC50 of 8 .mu.M for inhibition of HIV protease.

IT **130371-70-9P 130371-71-0P 130371-72-1P**
**130371-73-2P 130371-74-3P 130371-75-4P**
**130371-76-5P 130371-77-6P 130371-78-7P**
**130371-79-8P 130371-81-2P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as **HIV protease inhibitor**
)

L9 ANSWER 79 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1990:544869 CAPLUS

DN 113:144869

TI Structure-based, C2 symmetric inhibitors of HIV protease

AU Kempf, Dale J.; Norbeck, Daniel W.; Codacovi, LynnMarie; Wang, Xiu Chun; Kohlbrenner, William E.; Wideburg, Norman E.; Paul, Deborah A.; Knigge, Mark F.; Vasavanonda, Sudthida; et al.

CS Pharm. Prod. Div., Abbott Lab., Abbott Park, IL, 60064, USA

SO J. Med. Chem. (1990), 33(10), 2687-9
CODEN: JMCMAR; ISSN: 0022-2623

DT Journal

LA English

OS CJACS

AB Novel inhibitors of human immunodeficiency virus 1 (HIV-1) protease, an essential enzyme for the replication of HIV, are described. Based on the unique C2 sym., homodimeric structure of HIV protease, sym. and pseudosym. inhibitors were designed and synthesized. These compds. specifically inhibit HIV protease at subnanomolar concns. and block acute HIV infections in vitro at 20-150 nM.

IT **129467-48-7P 129467-49-8P 129467-50-1P**
**129491-63-0P 129491-64-1P 129491-65-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)

(prepn. and **HIV-1 protease inhibition** by)

L9 ANSWER 80 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1990:441332 CAPLUS
DN 113:41332
TI Preparation of peptide amides as human immunodeficiency virus inhibitors
IN Handa, Balraj Krishan; Machin, Peter James; Martin, Joseph Armstrong; Redshaw, Sally; Thomas, Gareth John
PA Hoffmann-La Roche, F., und Co. A.-G., Switz.
SO Eur. Pat. Appl., 69 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| PI | EP 346847 | A2 | 19891220 | EP 89-110717 | 19890613 |
| | EP 346847 | A3 | 19911023 | | |
| | EP 346847 | B1 | 19940511 | | |
| | R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| | US 5157041 | A | 19921020 | US 89-362621 | 19890605 |
| | ZA 8904285 | A | 19900228 | ZA 89-4285 | 19890606 |
| | AU 8936130 | A1 | 19891214 | AU 89-36130 | 19890607 |
| | AU 624144 | B2 | 19920604 | | |
| | HU 51254 | A2 | 19900428 | HU 89-2903 | 19890607 |
| | HU 205898 | B | 19920728 | | |
| | DK 8902863 | A | 19891214 | DK 89-2863 | 19890612 |
| | NO 8902407 | A | 19891214 | NO 89-2407 | 19890612 |
| | NO 175715 | B | 19940815 | | |
| | NO 175715 | C | 19941123 | | |
| | JP 02042048 | A2 | 19900213 | JP 89-149265 | 19890612 |
| | JP 2515019 | B2 | 19960710 | | |
| | FI 8902881 | A | 19891214 | FI 89-2881 | 19890613 |
| | FI 95693 | B | 19951130 | | |
| | FI 95693 | C | 19960311 | | |
| | AT 105549 | E | 19940515 | AT 89-110717 | 19890613 |
| | ES 2052815 | T3 | 19940716 | ES 89-110717 | 19890613 |
| | US 5446161 | A | 19950829 | US 92-916812 | 19920720 |
| | US 5554756 | A | 19960910 | US 95-391380 | 19950217 |
| | US 5652369 | A | 19970729 | US 95-394523 | 19950406 |
| | US 5620987 | A | 19970415 | US 95-398478 | 19950410 |

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| | GB 89-8035 | 19890410 |
| | US 89-362621 | 19890605 |
| | EP 89-110717 | 19890613 |
| | US 92-916812 | 19920720 |

OS MARPAT 113:41332

AB R1R2NCHR3CONHCHR4CR5R6CH2N(:O)nR7CHR8R9 [I; R1 = alkoxycarbonyl, aralkoxycarbonyl, (ar)alkanoyl, cycloalkylcarbonyl, aroyl, heterocyclylcarbonyl, alkylsulfonyl, etc.; R2 = H; R1R2N = cyclic arom. imide; R3 = (cyclo)alkyl, (aryl)alkyl, aryl, heterocyclylalkyl, cyanoalkyl, etc; R4 = alkyl, cycloalkyl(alkyl), aryl(alkyl); R5 = H; R6 = OH; R5R6 = :O; R7R8 = (un)substituted (CH2)3, (CH2)4, with 1 CH2 optionally replaced by NH, N(acyl), S, etc., optionally carrying 1 fused cycloalkane or (hetero)arom. ring; R9 = alkoxycarbonyl, monoalkylcarbamoyl, CONHCHR10CONHR11; R10, R11 = alkyl; n = 0, 1] and their pharmaceutically acceptable salts were prepd., e.g., by coupling amines H2NCHR4CR5R6CH2NR7CHR8R9 with acids R1R2NCHR3CO2H. Thus, N1-isobutyl-L-isoleucylamide (prepn. given) was coupled with Z-proline succinimide ester (Z = benzyloxycarbonyl), the resulting dipeptide was deprotected and coupled with (Z-phenylalanyl)methyl bromide, the intermediate tripeptide reduced by NaBH4 in EtOH, deprotected, and coupled with Z-Asn-OH to give N2-[N-[3(S)-[(Z-asparaginyl)amino]-2(R,S)-hydroxy-4-phenylbutyl]-L-prolyl]-N1-isobutyl-L-isoleucylamide. One (unspecified) of 2 isomers of the latter in vitro inhibited human immunodeficiency virus protease with an IC50 of 0.13 .mu.M. IC50 values reported for 7 other I ranged from 0.01-0.87 .mu.M.

IT **127749-93-3P 127749-94-4P 128018-12-2P**
**128018-26-8P 128018-42-8P 128018-49-5P**
**128018-67-7P 128018-74-6P 128018-75-7P**
**128018-76-8P 128018-77-9P 128018-78-0P**
**128018-89-3P 128018-91-7P 128018-92-8P**
**128018-93-9P 128018-94-0P 128018-95-1P**
**128018-96-2P 128018-97-3P 128018-98-4P**
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**128019-76-1P 128019-82-9P 128019-94-3P**
**128043-05-0P 128043-06-1P 128053-23-6P**
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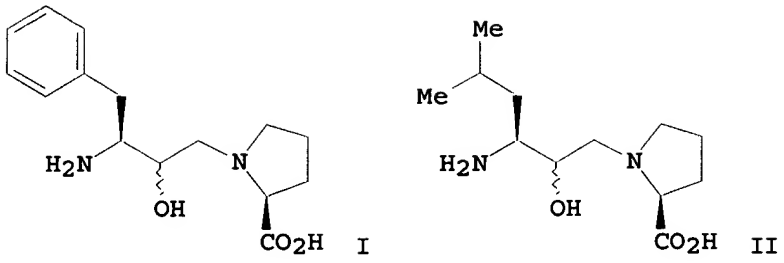
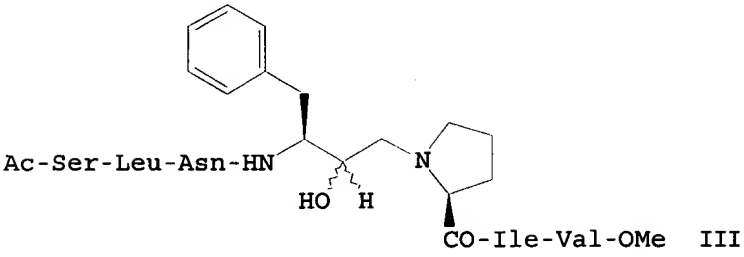
**128053-33-8P 128053-40-7P 128053-42-9P**
**128053-46-3P 128111-39-7P 128111-40-0P**
**128111-44-4P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as **HIV protease inhibitor**
)

L9 ANSWER 81 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1990:417492 CAPLUS
DN 113:17492
TI Rational design of peptide-based HIV proteinase inhibitors

AU Roberts, Noel A.; Martin, Joseph A.; Kinchington, Derek; Broadhurst, Anne V.; Craig, J. Charles; Duncan, Ian B.; Galpin, Sarah A.; Handa, Balraj K.; Kay, John; et al.
CS Roche Prod. Ltd., Welwyn Garden City/Hertfordshire, AL7 3AY, UK
SO Science (Washington, D. C., 1883-) (1990), 248(4953), 358-61
CODEN: SCIEAS; ISSN: 0036-8075
DT Journal
LA English
AB A series of peptide derivs. based on the transition-state mimetic concept has been designed that inhibit the proteinase from the human immunodeficiency virus (HIV). The more active compds. inhibit both HIV-1 and HIV-2 proteinases in the nanomolar range with little effect at 10 micromolar against the structurally related human aspartic proteinases. Proteolytic cleavage of the HIV-1 gag polyprotein (p55) to the viral structural protein p24 was inhibited in chronically infected CEM cells. Antiviral activity was obsd. in the nanomolar range (with one compd. active below 10 nanomolar) in three different cell systems, as assessed by p24 antigen and syncytium formation. Cytotoxicity was not detected at 10 and 5 micromolar in C8166 and JM cells, resp., indicating a high therapeutic index for this new class of HIV proteinase inhibitors.
IT **127749-93-3 127749-94-4 127749-95-5**
**127779-20-8**
RL: BIOL (Biological study)
(as **human immunodeficiency virus proteinase inhibitor**, antiviral activity and cytotoxicity of, structure in relation to)

L9 ANSWER 82 OF 82 CAPLUS COPYRIGHT 1999 ACS
AN 1990:406798 CAPLUS
DN 113:6798
TI Hydroxyethylamine analogs of the p17/p24 substrate cleavage site are tight-binding inhibitors of HIV protease
AU Rich, Daniel H.; Green, Jeremy; Toth, Mihaly V.; Marshall, Garland R.; Kent, Stephen B. H.
CS Sch. Pharm., Univ., Madison, WI, 53706, USA
SO J. Med. Chem. (1990), 33(5), 1285-8
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CASREACT 113:6798; CJACS
GI




AB Hydroxyethylamine (HEA) dipeptidyl isosteres I and II were designed to mimic the tetrahedral intermediate for the hydrolysis of Tyr-Pro, one of the partial substrate sequences cleaved by HIV protease. Incorporation of hydroxyethylamines I and II in peptides related to the p17/p24 substrate sequence produces tight-binding inhibitors of HIV protease. HEA inhibitor III has a Ki = 0.66 nM.

IT **127231-45-2P 127231-46-3P 127231-47-4P**
**127231-48-5P 127231-49-6P 127231-50-9P**
**127231-51-0P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as **HIV protease inhibitor**
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E1 THROUGH E944 ASSIGNED

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DICTIONARY FILE UPDATES: 28 JAN 99 HIGHEST RN 217939-24-7

TSCA INFORMATION NOW CURRENT THROUGH JUNE 29, 1998

Please note that search-term pricing does apply when conducting SmartSELECT searches.

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Searcher : Shears 308-4994

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Searcher : Shears 308-4994

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=> d scan

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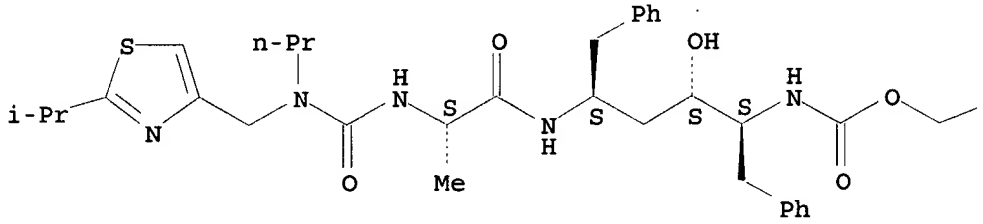
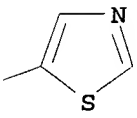
L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN 2,7,10,12-Tetraazapentadecanoic acid, 4-hydroxy-9-methyl-12-[[2-(1-methylethyl)-4-thiazolyl]methyl]-8,11-dioxo-3,6-bis(phenylmethyl)-, 5-thiazolylmethyl ester, [3S-(3R*,4R*,6R*,9R*)]- (9CI)
MF C37 H48 N6 O5 S2

Absolute stereochemistry.

PAGE 1-A




PAGE 1-B

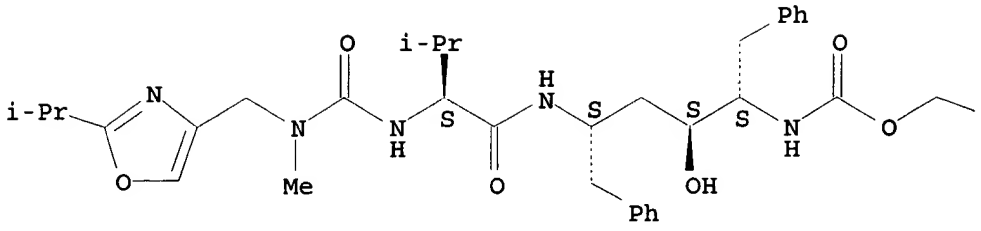



HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):24

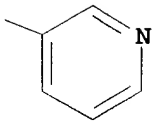
L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-oxazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 3-pyridinylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]- (9CI)
MF C39 H50 N6 O6

Absolute stereochemistry.

PAGE 1-A

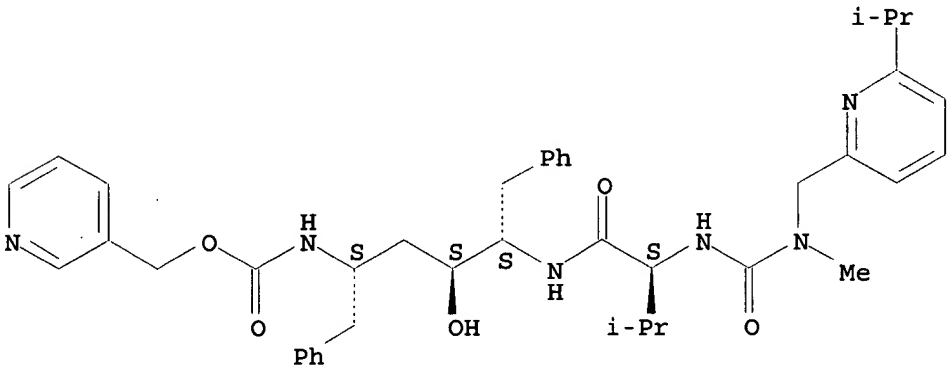


PAGE 1-B



L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN 2,4,7,12-Tetraazatridecan-13-oic acid, 9-hydroxy-2-methyl-5-(1-methylethyl)-1-[6-(1-methylethyl)-2-pyridinyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 3-pyridinylmethyl ester, [5S-(5R*,8R*,9R*,11R*)]-(9CI)
MF C41 H52 N6 O5

Absolute stereochemistry.

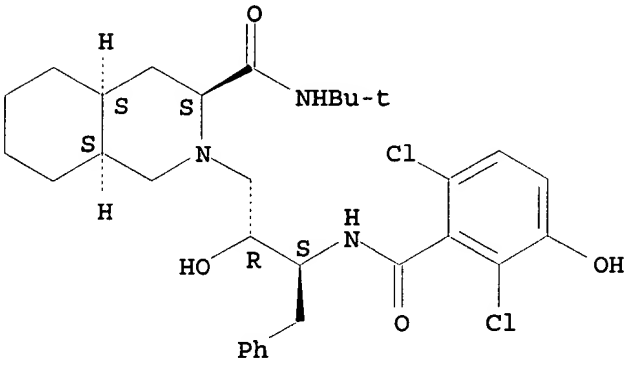


L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN 3-Isoquinolinecarboxamide, 2-[3-[(2,6-dichloro-3-

hydroxybenzoyl)amino]-2-hydroxy-4-phenylbutyl]-N-(1,1-dimethylethyl)decahydro-, [3S-[2(2S*,3R*),3.alpha.,4a.beta.,8a.beta.]]- (9CI)

MF C31 H41 Cl2 N3 O4

Absolute stereochemistry.



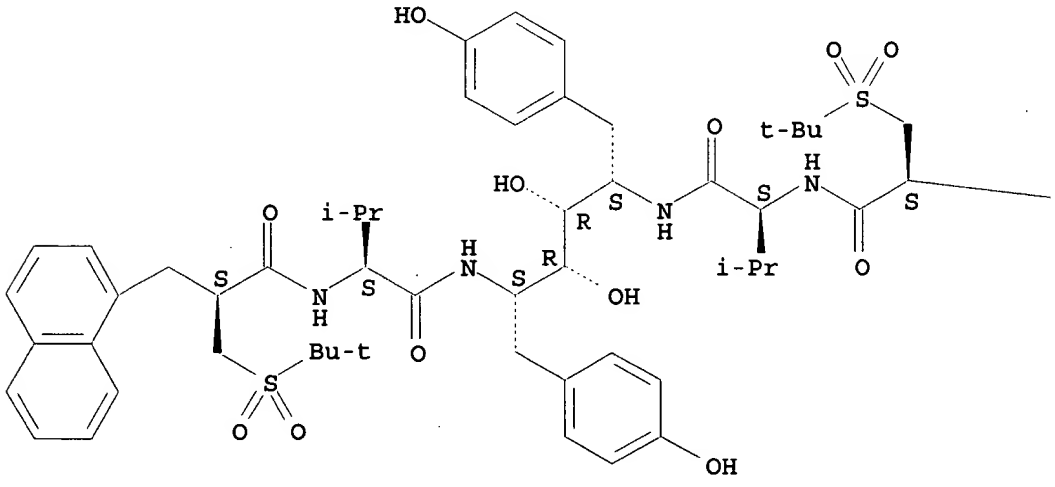
L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS

IN L-Iditol, 1,2,5,6-tetradeoxy-2,5-bis[[2-[[2-[[(1,1-dimethylethyl)sulfonyl]methyl]-3-(1-naphthalenyl)-1-oxopropyl]amino]-3-methyl-1-oxobutyl]amino]-1,6-bis(4-hydroxyphenyl)-, [2[S(S)],5[S(S)]]- (9CI)

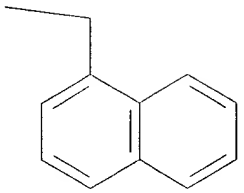
MF C64 H82 N4 O12 S2

Absolute stereochemistry.

PAGE 1-A

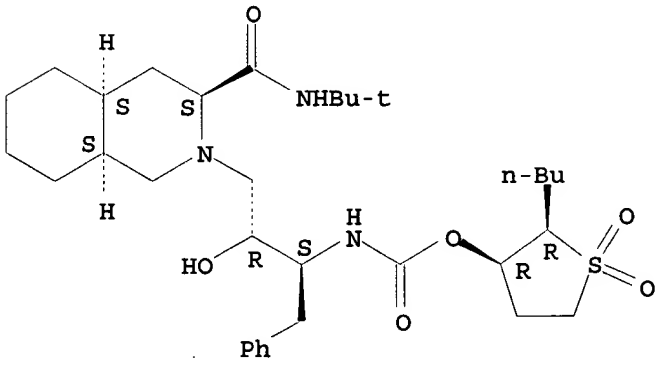


Searcher : Shears 308-4994



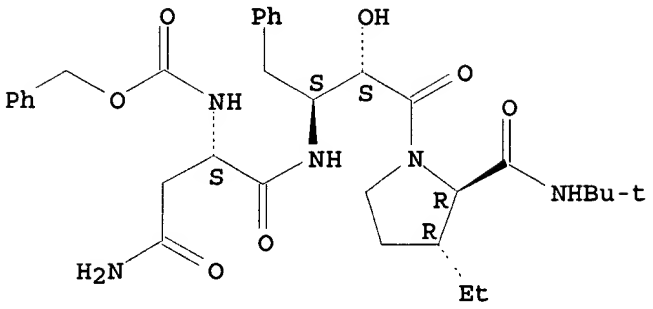
L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN Carbamic acid, [3-[3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]-, 2-butyltetrahydro-1,1-dioxido-3-thienyl ester, [3S-[2[1R*(2S*,3S*),2S*],3.alpha.,4a.beta.,8a.beta.]]- (9CI)
MF C33 H53 N3 O6 S

Absolute stereochemistry.




L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN Carbamic acid, [3-amino-1-[[[3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3-ethyl-1-pyrrolidinyl]-2-hydroxy-3-oxo-1-(phenylmethyl)propyl]amino]carbonyl]-3-oxopropyl]-, phenylmethyl ester, [2R-[1[1S*(S*),2S*],2.alpha.,3.beta.]]- (9CI)
MF C33 H45 N5 O7

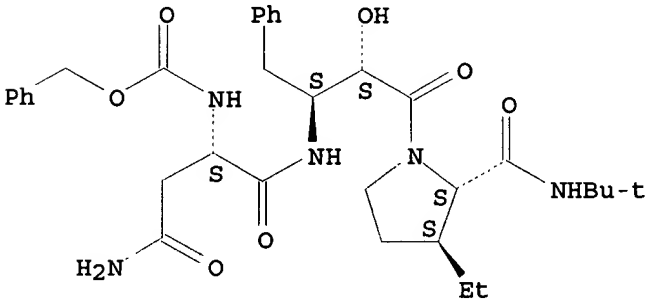
Absolute stereochemistry.



CBZ- Asn

L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN Carbamic acid, [3-amino-1-[[[3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3-ethyl-1-pyrrolidinyl]-2-hydroxy-3-oxo-1-(phenylmethyl)propyl]amino]carbonyl]-3-oxopropyl]-, phenylmethyl ester, [2S-[1[1R*(R*),2R*],2.alpha.,3.beta.]]- (9CI)
MF C33 H45 N5 O7

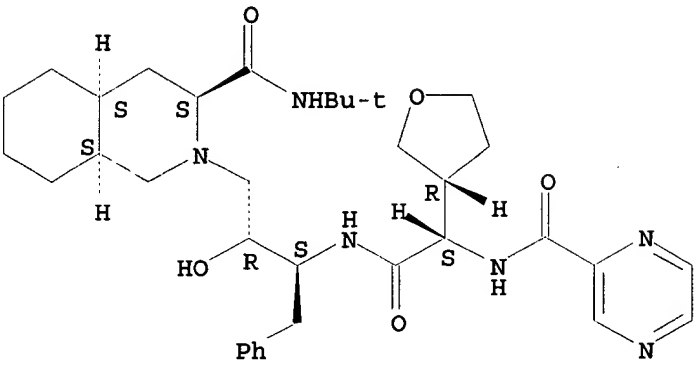
Absolute stereochemistry.



L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN 3-Isoquinolinecarboxamide, N-(1,1-dimethylethyl)decahydro-2-[2-hydroxy-4-phenyl-3-[[[(pyrazinylcarbonyl)amino](tetrahydro-3-furanyl)acetyl]amino]butyl]-, [3S-[2[2S*,3R*[R*(S*)]],3.alpha.,4a.beta.,8a.beta.]]- (9CI)
MF C35 H50 N6 O5

Searcher : Shears 308-4994

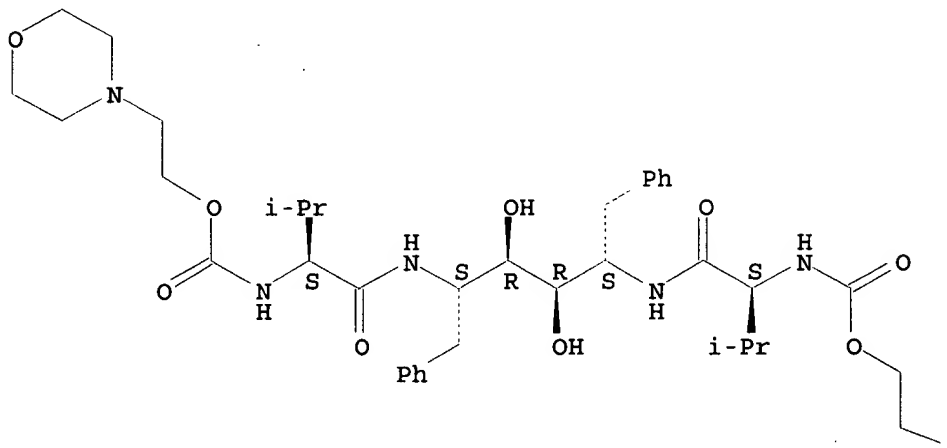
Absolute stereochemistry.



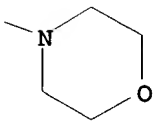
L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN L-Iditol, 1,2,5,6-tetradeoxy-2,5-bis[[3-methyl-2-[[[2-(4-morpholinyl)ethoxy]carbonyl]amino]-1-oxobutyl]amino]-1,6-diphenyl-, [2(S),5(S)]- (9CI)
MF C42 H64 N6 O10

Absolute stereochemistry.

PAGE 1-A

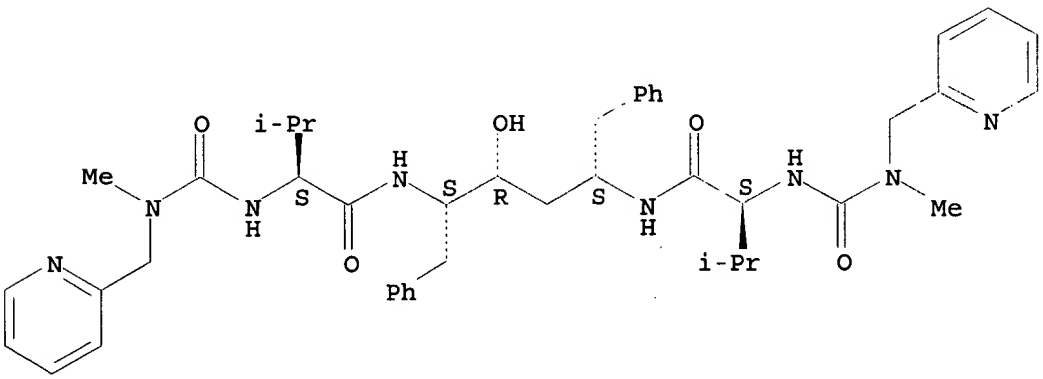


Searcher : Shears 308-4994



L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN 2,5,10,13-Tetraazatetradecanediamide, 7-hydroxy-N,N'-dimethyl-3,12-bis(1-methylethyl)-4,11-dioxo-6,9-bis(phenylmethyl)-N,N'-bis(2-pyridinylmethyl)-, [3S-(3R*,6R*,7S*,9R*,12R*)]- (9CI)
MF C44 H58 N8 O5

Absolute stereochemistry.

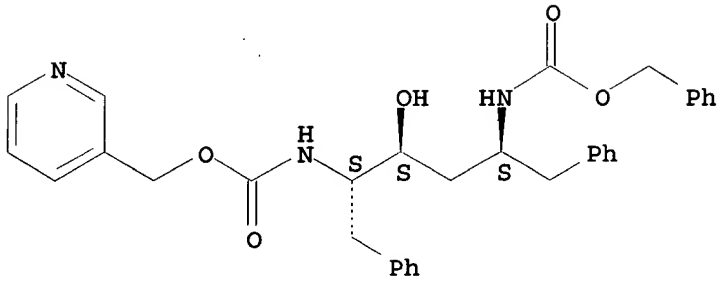


L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN Carbamic acid, [2-hydroxy-5-phenyl-4-[[(phenylmethoxy)carbonyl]amino]-1-(phenylmethyl)pentyl]-, 3-pyridinylmethyl ester,

Searcher : Shears 308-4994

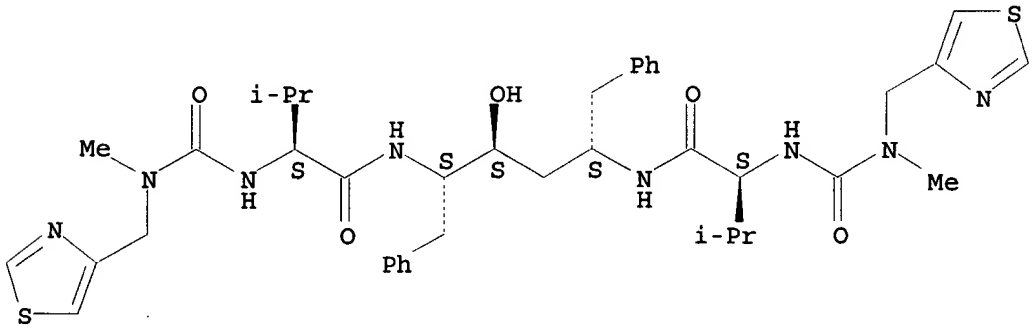
[1S-(1R*,2R*,4R*)]- (9CI)
MF C33 H35 N3 O5

Absolute stereochemistry.



L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN 2,5,10,13-Tetraazatetradecanediamide, 7-hydroxy-N,N'-dimethyl-3,12-bis(1-methylethyl)-4,11-dioxo-6,9-bis(phenylmethyl)-N,N'-bis(4-thiazolylmethyl)-, [3S-(3R*,6R*,7R*,9R*,12R*)]- (9CI)
MF C40 H54 N8 O5 S2

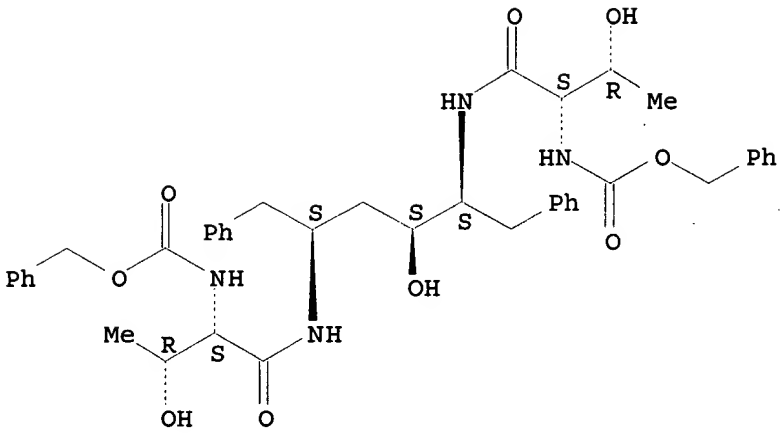
Absolute stereochemistry.



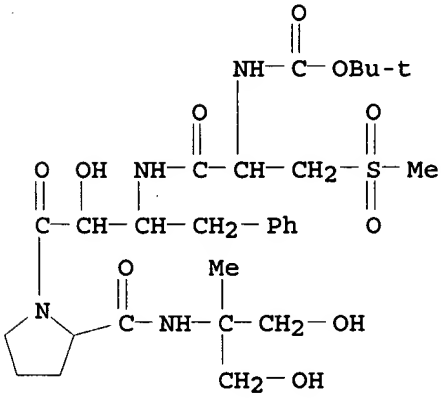
L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN 2,5,10,13-Tetraazatetradecanedioic acid, 7-hydroxy-3,12-bis(1-hydroxyethyl)-4,11-dioxo-6,9-bis(phenylmethyl)-, bis(phenylmethyl) ester, [3S-[3R*(S*),6R*,7R*,9R*,12R*(S*)]]- (9CI)
MF C42 H50 N4 O9

Absolute stereochemistry.

Searcher : Shears 308-4994

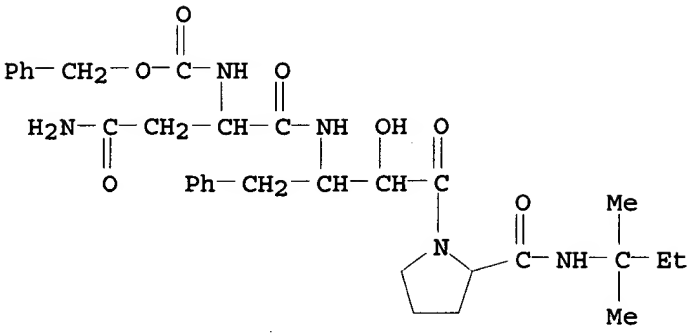


L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN L-Prolinamide, N-[(1,1-dimethylethoxy)carbonyl]-3-(methylsulfonyl)-L-alanyl-(2S,3S)-2-hydroxy-4-phenyl-3-aminobutanoyl-N-[2-hydroxy-1-(hydroxymethyl)-1-methylethyl]- (9CI)
SQL 4
MF C28 H44 N4 O10 S



L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN L-Prolinamide, N2-[(phenylmethoxy)carbonyl]-L-asparaginyl-(2S,3S)-2-hydroxy-4-phenyl-3-aminobutanoyl-N-(1,1-dimethylpropyl)- (9CI)

MF C32 H43 N5 O7



L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN L-Isoleucinamide, 1-[3-[[4-amino-1,4-dioxo-2-[[(phenylmethoxy)carbonyl]amino]butyl]amino]-2-hydroxy-4-phenylbutyl]-L-prolyl-N-[2-(2-pyridinyl)ethyl]-, [2R-[2R*,3S*(S*)]]-(9CI)
MF C40 H53 N7 O7

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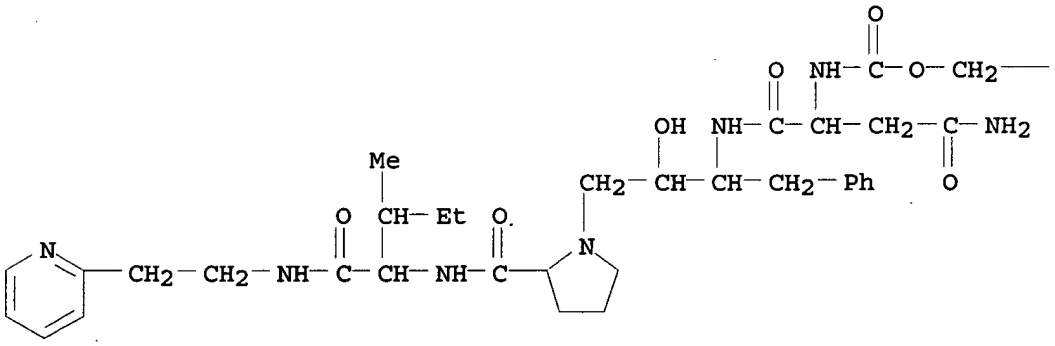
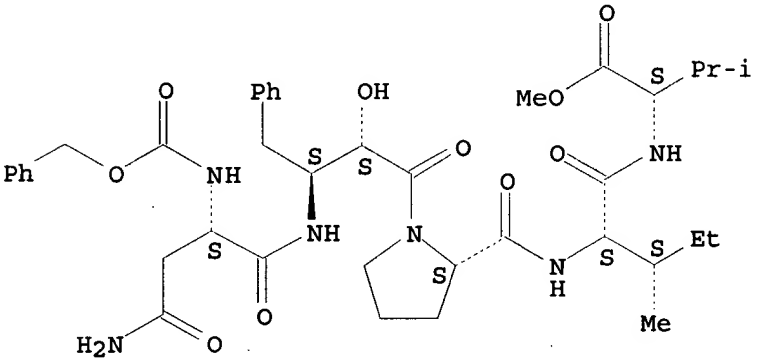


PAGE 1-B

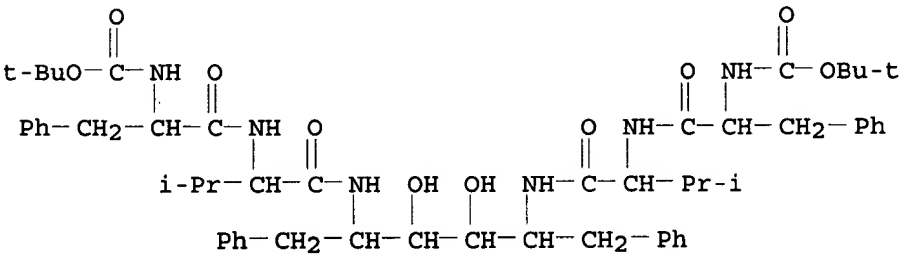
— Ph

IN L-Valine, N2-[(phenylmethoxy)carbonyl]-L-asparaginyl-(2S,3S)-2-hydroxy-4-phenyl-3-aminobutanoyl-L-prolyl-L-isoleucyl-, methyl ester (9CI)
SQL 5
MF C39 H54 N6 O10

Absolute stereochemistry.

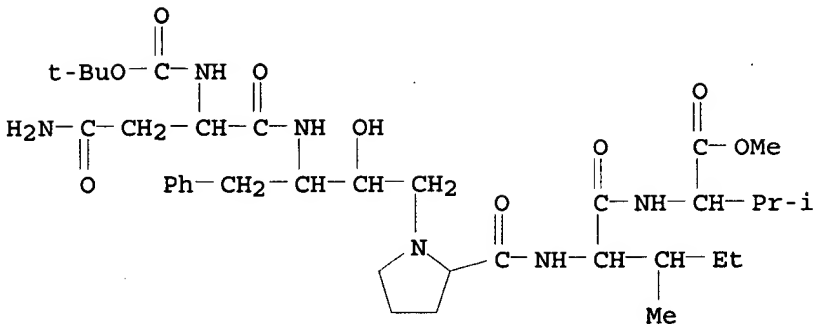


L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN L-Iditol, 1,2,5,6-tetradeoxy-2,5-bis[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-valyl]amino]-1,6-diphenyl- (9CI)
MF C56 H76 N6 O10



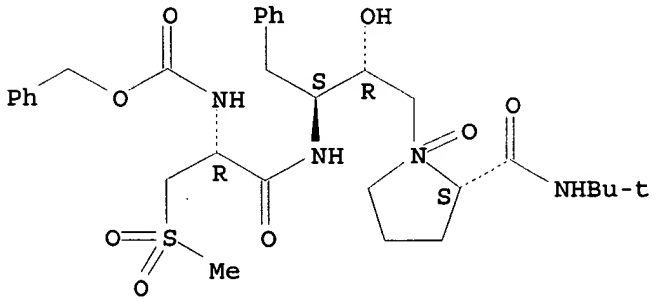
L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN L-Valine, N-[N-[1-[3-[[4-amino-2-[[(1,1-dimethylethoxy)carbonyl]amino]-1,4-dioxobutyl]amino]-2-hydroxy-4-phenylbutyl]-L-prolyl]-L-isoleucyl]-, methyl ester, [2R-[2R*,3S*(S*)]]- (9CI)
MF C36 H58 N6 O9

Searcher : Shears 308-4994



L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN Carbamic acid, [2-[[3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-1-oxido-1-pyrrolidinyl]-2-hydroxy-1-(phenylmethyl)propyl]amino]-1-[(methylsulfonyl)methyl]-2-oxoethyl]-, phenylmethyl ester, [2S-[1[1R*(S*),2S*],2R*]]- (9CI)
MF C31 H44 N4 O8 S

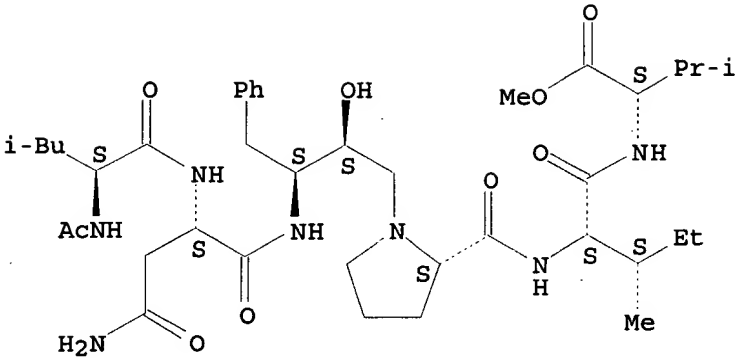
Absolute stereochemistry.



L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN L-Valine, N-[N-[1-[3-[[N2-(N-acetyl-L-leucyl)-L-asparaginyl]amino]-2-hydroxy-4-phenylbutyl]-L-prolyl]-L-isoleucyl]-, methyl ester, [S-(R*,R*)]- (9CI)
SQL 6
MF C39 H63 N7 O9

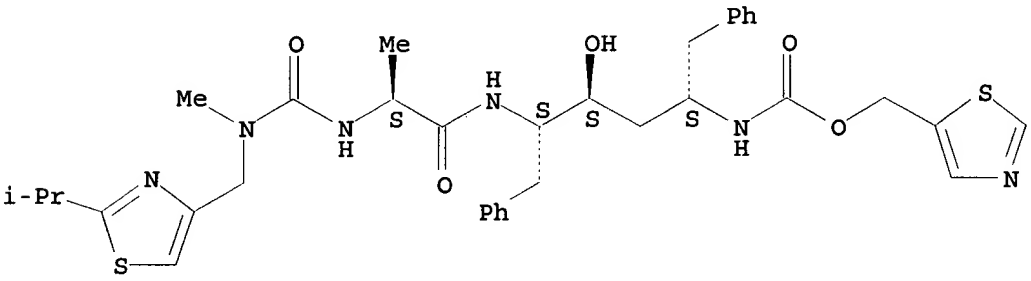
Absolute stereochemistry.

Searcher : Shears 308-4994



L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN 2,4,7,12-Tetraazatridecan-13-oic acid, 9-hydroxy-2,5-dimethyl-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, [5S-(5R*,8R*,9R*,11R*)]- (9CI)
MF C35 H44 N6 O5 S2

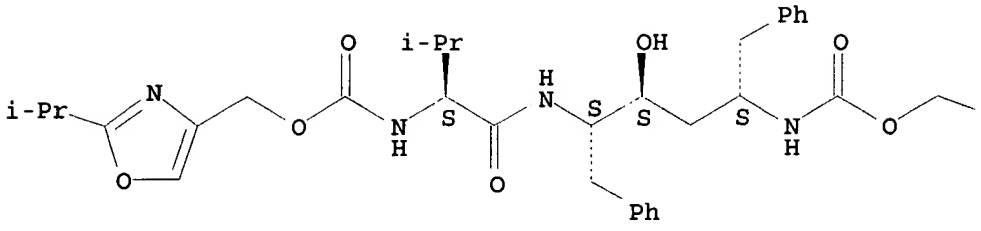
Absolute stereochemistry.



L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN 2-Oxa-4,7,12-triazatridecan-13-oic acid, 9-hydroxy-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-oxazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 3-pyridinylmethyl ester, [5S-(5R*,8R*,9R*,11R*)]- (9CI)
MF C38 H47 N5 O7

Absolute stereochemistry.

PAGE 1-A



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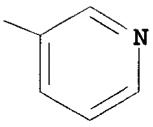
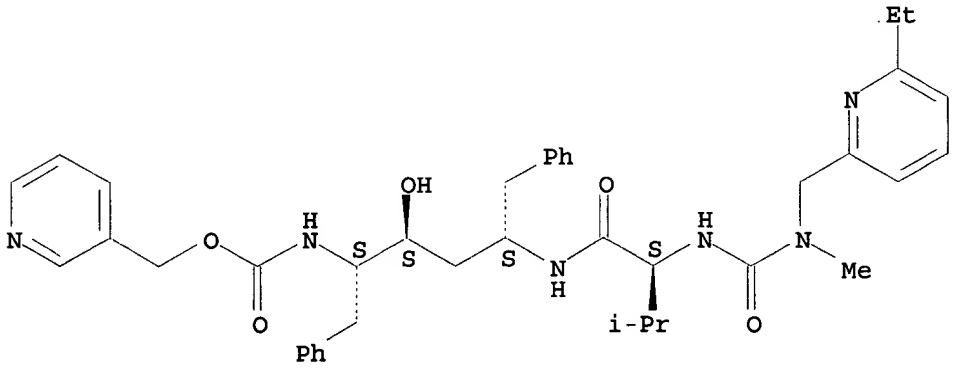


L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS
IN 2,4,7,12-Tetraazatridecan-13-oic acid, 1-(6-ethyl-2-pyridinyl)-10-hydroxy-2-methyl-5-(1-methylethyl)-3,6-dioxo-8,11-bis(phenylmethyl)-, 3-pyridinylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]- (9CI)
MF C40 H50 N6 O5

Absolute stereochemistry.



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